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Synthetic Studies Towards The Stellettins

Tung Yin Lin
Eastern Illinois University

SYNTHETIC STUDIES TOWARDS THE STELLETINS

LIN

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SYNTHETIC STUDIES TOWARDS THE STELLETTINS

BY

TUNG YIN LIN

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SYNTHETIC STUDIES TOWARDS THE STELLETTINS

BY

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Synthetic Studies of Towards the Stellettins

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Abstract

The synthesis of the stellettins, differing in the side chain at the C-13 position of the tricyclic region, was attempted by attaching the C-ring to a Wieland-Miescher ketone core using 1,3-bisphosphonoacetone. The decalin precursor was prepared in 35% from condensing ethyl acetate with acrolein, and a MnO_2 oxidation, but too little material was obtained to cyclize this into the decalin. An alternative route involving a 2-step Robinson annulation of 2-methyl-1,3 cyclohexanedione with ethyl or methyl vinyl ketone and L-phenylalanine catalysis, followed by protecting C-9 carbonyl with acetal, gave 29% and 14% yields respectively.

1,3-Bisphosphonoacetone was prepared in a 3-step synthesis from 1,3-dichloroacetone in 6% yield. Selective monocondensation reaction of bisphosphonate with benzaldehydes and cinnamaldehydes were successful in yielding the phosphonoenone products in 31-67% yields. Cyclization of the C-ring using the bisphosphonate was modeled using the tosylate of 2,2-dimethyl cyclohexanone. This was prepared in 35% yield using [hydroxy(tosyloxy)iodo]benzene, and the tosylation reaction furthermore was shown to be successful at secondary α-carbonyl but not at tertiary centers. However, the phosphonate substitution reactions suggested that the tosylate is too

sterically hindered for encumbering substitution to occur, whereas smaller leaving group such as mesylate or chloride gave the condensation product.

List of Figures and Tables

Introduction

The stellettins (Figure 1) are a new type of triterpenoids isolated from sea marine sponges of genra *Stelletta*, *Jaspis* and *Rhabdastrella*.[1] The malabaricanes are a set of yellow pigments originally isolated from the tree *Alianthus malabarica*,[2] and characterized by a tricyclic 3a,6,6,9-tetramethyl-3-(1,5,9-trimethyldecyl)perhydro-benz[e]-indene system with a *trans-anti-trans* stereochemistry of the 6-6-5 tricyclic core. More recent research[3] reported the discovery of two new triterpenes called stellettins A (**1**) and B (**2**), which were isolated from the methanol extract of the sponge *Stelletta tenuis*. Characterization of these compounds revealed a similar malabaricane-like structure with a 6-6-5 tricyclic core, but having a *trans-syn-trans* ring fusion system. These compounds also contained an oxygenation at C-3, a keto group at C-12 and a tridecyl side chain at C-13. These features define a new rare category of secondary compounds referred to as the isomalabaricanes.

These isomalabaricane triterpenoids could be further divided into three groups: (1) the stellettins, (2) the stelliferins,[4] and (3) the globostellatic acids.[5] The stellettins terminate either in a pyrone group or a carboxylic acid, and have a dimethyl substituent at C-4. The stellettins were isolated as pairs of stereoisomers; for example stellettin A, with a C-13 *E*-olefin at the juncture of the tricyclic core and the side chain was isolated alongside stellettin B that had a C-13 *Z*-configuration. These stereoisomers rapidly isomerize into each other under exposure to light. Stellettins C (**3**), D (**4**), E (**5**), F (**6**) and G (**7**) were later isolated from another extraction of a *Stelletta sp.* (Stellettidae). There are currently eleven stellettins reported so far, and the latest stellettins discovered were stellettins L (**8**) and M (**9**)[6] from *S. tenuis*.

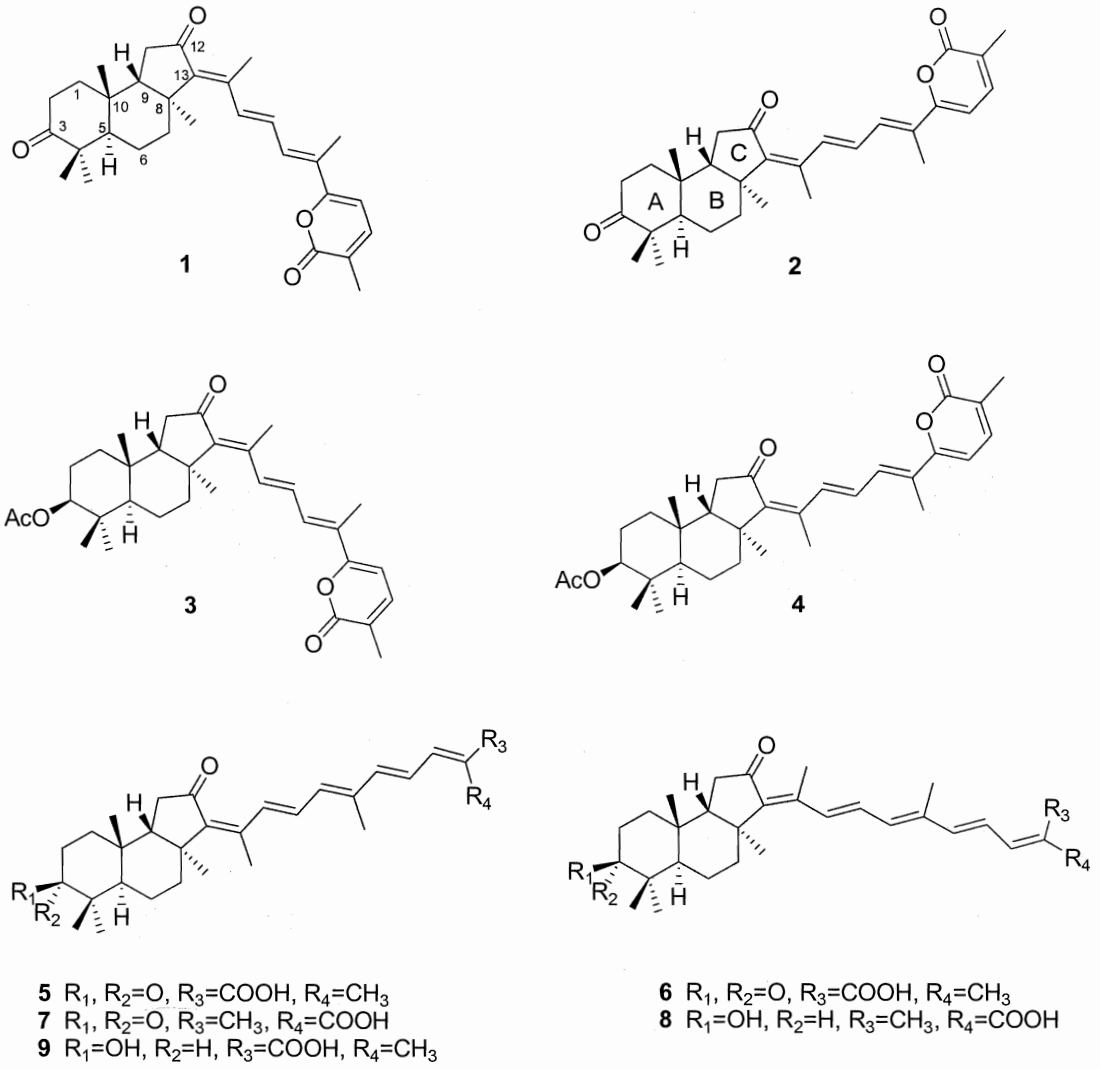


Figure 1. Stellettins A-G, L and M.

The stelliferins are characterized by a C-22 oxygenation on the side chain, such as a hydroxyl group, while the globostellatic acids have an A ring with C-4 carboxylation, an α C-3 hydroxyl group, and a terminal hydroxyl group on the side chain (Figure 2). There are other related natural compounds such as jaspolides that are not triterpenoids,[7] but still contain the general tricyclic skeleton plus an unsaturated side chain. In short, the main difference between these isomalabaricanes is in their side chains.

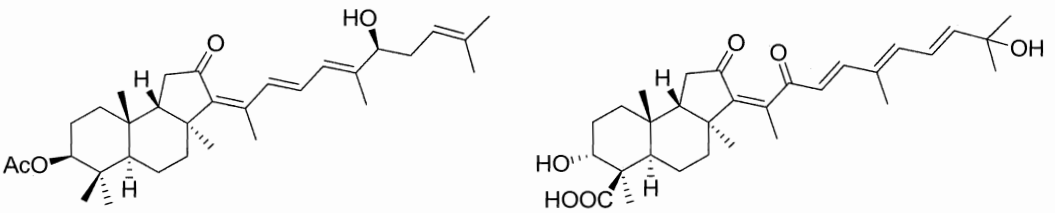


Figure 2. A representative stelliferin and globostellatic acid.

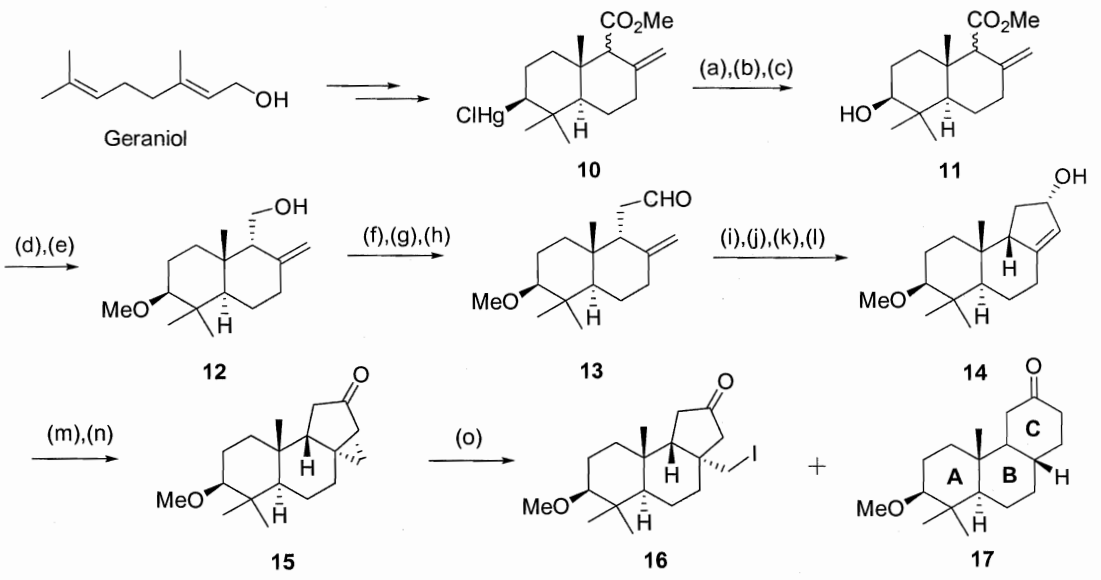
As for the activity, the stellettins showed a superior cytotoxicity effect against human leukemia cells.[3] Stellettins A and B had an ED_{50} of only 0.001μg/mL against P388 leukemia cells. Further cytotoxicity tests from the NCI suggested that stellettins A/B were more potent against leukemia cells than stellettins E/F, while stellettins C/D were even more effective. The stellettins are also highly cytotoxic against several key tumor cell types in the 60 cell line screen, for example stellettins C/D were most effective against leukemia, CNS and renal cancer cell lines, and had an average GI_{50} of only 0.09 μg/mL from all cells. The newly discovered stellettins L and M exhibited superior cytotoxic abilities (IC_{50}<0.01 μg/mL against P388 leukemia cells). The globostellatic acids and stelliferins are also highly cytotoxic. For example, globostellatic acids A-D have IC_{50}'s ranging from 0.1 to 0.46 μg/mL,[5] and 29-hydroxystelliferin D has an IC_{50} of 0.19μg/mL.[4]

The mechanism of how stellettins cause cytotoxicity is not fully understood. However, probing the infected cells suggested that the stellettins trigger apoptosis.[8] Apoptosis is a programmed cell death event that the organism signals to kill old cells. The stellettins are believed to activate NADPH oxidase, which generates several reactive species that cause apoptosis factors to be released from the mitochondria, and overall activate apoptosis.

The remarkable cytotoxic abilities of the stellettins against human cancer cells is

very valuable for pharmaceutical research. They could serve as compounds for the development of effective treatments of tumor cells. However, the stellettins are only found from deep sea marine sponges, and the extraction and separation methods are troublesome and expensive, involving repetitive column chromatography or HPLC and consuming lots of solvent. Additionally, the overall yield of stellettins from the extraction was merely 1mg of each stellettins per 1kg of sponge.[1] All these factors lower the practical use of the isolated stellettins for medical research. Therefore, this research aimed at utilizing organic synthetic methods to prepare the stellettins in the lab.

The synthesis of the stellettins was originally attempted by Heissler's group, who investigated preparing the tricyclic portion (Figure 3).[9] Their strategy first involved synthesis of a decalin, followed by an acid-catalyzed ring closure of an aldehyde and olefin to form the C-ring. The decalin starting material **10** could be prepared in 5 steps from the commercially available linear molecule geraniol by Weiler's method.[10] The chloromercury group was treated with borohydride, and oxidation gave a mixture of diastereomeric decalins, which were reduced by $NaBH_4$ to give enantiomeric pure hydroxyl decalin **11**. The hydroxyl group was then directly methylated, followed by reduction of the carboxylate group to give alcohol **12**. The alcohol group was substituted with a nitrile via the mesylate, which was then reduced to aldehyde **13** by DIBAL. Dimethylaluminum chloride catalyzed cyclization and olefin rearrangement gave the key tricyclic core **14** in 66% yield. This underwent a Furukawa's modification of the Simmons-Smith cyclopropanation, and was followed by ruthenium mediated oxidation to give ketone **15**. Opening the cyclopropyl ring with trimethylsilyl iodide gave a 6:4 mixture of the cyclopentyl C-ring compound **16** and the cyclohexyl C-ring compound **17** due to poor regioselectivity of the α,β-carbonyl bonds. The overall yield of these 17 steps was 5.3%.



(a) $NaBH_4$, O_2, DMF; (b) $(COCl)_2$, DMSO, CH_2Cl_2; (c) $NaBH_4$, EtOH; (d) $KN(SiMe_3)_2$, MeI, THF;

(e) $LiAlH_4$, ether; (f) MsCl, NEt_3, CH_3Cl_2; (g) NaCN, DMSO; (h) $(i\text{-}Bu)_2AlH$, toluene; (i) Me_2AlCl, CH_2Cl_2; (j) $n\text{-}Pr_4NRuO_4$, NMO; (k) Na_2CO_3, MeOH; (l) $NaBH_4$, $CeCl_3$, MeOH; (m) ICH_2Cl, $ZnEt_2$, $(CH_2Cl)_2$;

(n) $n\text{-}Pr_4NRuO_4$, NMO; (o) Me_3SiI, CCl_4.

Figure 3. Heissler's synthesis of the tricyclic core for stellettins.

Some limitations to Heissler's method are that the cyclopropane ring opening step only gave 60% of the 6-6-5 member ring core, with significant yield of byproducts, and the reduction of the iodide from **16** to give the C-8 CH_3 group was difficult. They successfully obtained compound **16** but could not go any further. In addition, this method gives an intermediate that lacks functionalization at C-13, which might make it difficult to regioselectively add the side chain.

Another approach toward the tricyclic core system was developed by the Meyers'

group.[11] It started with alkylating a chiral bicyclic lactam **18** with 2-(2-bromophenyl)-1-iodoethane (**19**), followed by direct methylation with MeI to form the enantiomeric pure lactam **21** (81% ee) (Figure 4). Under basic conditions, lactam **21** formed an aryllithium that nulecophilically attacked the amide carbonyl and cyclized the second ring to give decalin **22** as an intermediate. After hydrolytic cleavage of the chiral auxiliary portion, decalin **23** was treated with a base and an Aldol condensation cyclized it into tricyclic core **24**, with an overall yield of 64% over 5 steps. However, this method also lacked a functionality at C-13 for side chain addition, as well as for the variability of the A ring.

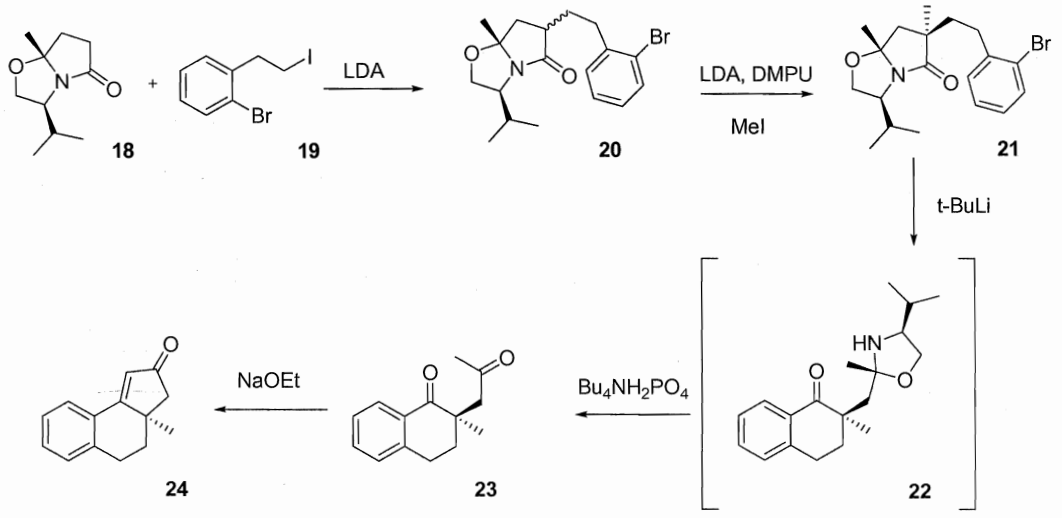


Figure 4. Meyers' synthesis of the tricyclic core for stellettins.

To develop a novel synthesis of the stellettins, a new retrosynthetic scheme (Figure 5) was proposed for a general stellettin (**25**) consisting of the *trans-syn-trans* tricyclic core and a C-13 side chain. The retrosynthesis would allow for variations at C-3 of the tricyclic core, the side chain, and the C-13 stereochemistry. The last step would involve adding the side chain to the tricyclic core, and this would be preferred since various stellettins can utilize the same synthetic scheme until the last step and prevent isomerization of the C-13 olefin occurring throughout the reaction sequence. The

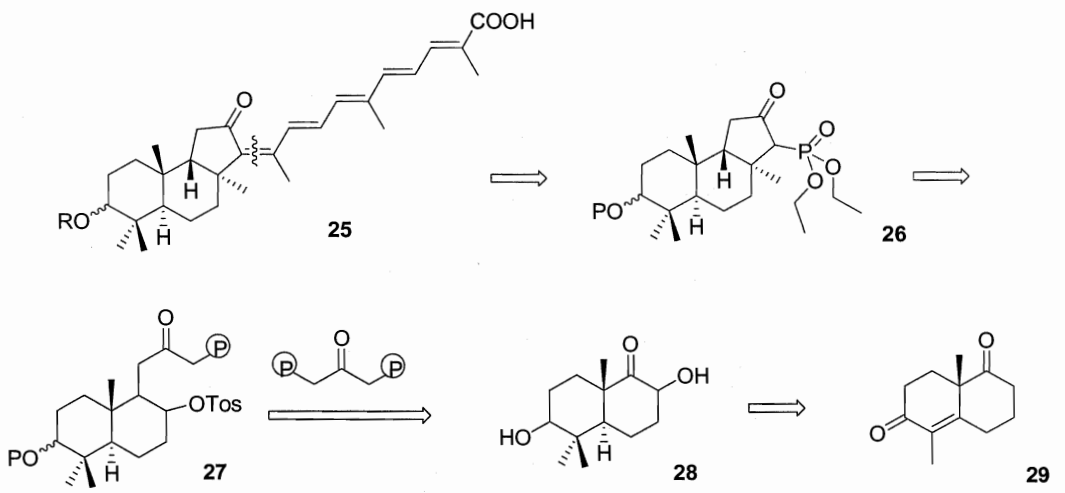


Figure 5. Retrosynthetic scheme for preparation of the stellettins.

attachment of the two species would rely on the phosphonate group at C-13 in the tricyclic core **26** undergoing a Wittig-like reaction with the appropriate carbonyl side chain partner. The development of this tricyclic core **26** was the main goal for this research since it introduces new methodology and is more challenging than making the side chain. In order to synthesize core **26**, first a decalin system will be constructed and then cyclized to give the C-ring. The cyclization strategy will utilize a S_N2 reaction of the phosphonate carbanion with a good leaving group at C-8 of decalin **27** to close the C-ring. The nucleophilic carbon is α to both the carbonyl and phosphonyl groups, making the protons fairly acidic and so it should serve as a nucleophile upon deprotonation. However, the nucleophilic substitution of a phosphonate on a cyclohexyl leaving group has not yet been reported, therefore this technique needs to be tested with model reactions beforehand. Decalin **27** could be prepared from ketone **28** with a Wittig-like condensation with a bisphosphonate, followed by reduction of the double bond at C-9. The leaving group in decalin **27** could possibly be installed from the hydroxyl group in decalin **28**, which would be added by oxidation α to the C-8 carbonyl in decalin **29**. Decalin **29** is the Wieland-Miescher ketone, which is a well known dioxo decalin and has been widely used as a precursor for a terpenoid synthesis.[12] The formation of Wieland-Miescher ketone by

an Aldol reaction would be the starting point for this synthetic scheme.

The most uncertain part of this synthetic scheme is the phosphonate chemistry. To install the phosphonate onto the decalin system, a Wittig-like condensation reaction of phosphonate would be utilized. Horner-Wadsworth-Emmons (HWE) condensation reactions[13] occur similar to the Aldol reaction (Figure 6), where a phosphonyl enolate attacks a carbonyl species to form a new C-C bond, and a phosphonic acid is eliminated to form the olefin.

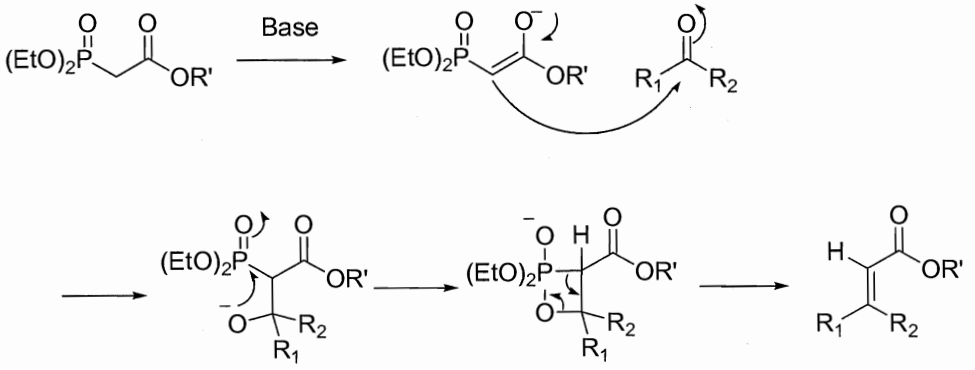


Figure 6. The mechanism of a HWE condensation reaction.

HWE condensations have been widely used in cyclization reactions to prepare polycyclic terpenes. For instance, in Heissler's synthesis of the 6,6,6 *trans-syn-trans* tricyclic core system[14] (Figure 7), decalin **30** was treated with LiCl and DBU in an intramolecular reaction to complete the formation of enone **31**. However in this study, since one phosphonyl group will be consumed in the HWE condensation to install the phosphonyl component onto the decalin core, one more phosphonyl group is needed for the substitution reaction to close the ring. Cyclization using two a 1,3-bisphosphonate was firstly utilized by Büchi and Wüest to synthesize macrocyclic ketones such as cyclopentadienone **33** from linear phosphonate **32** (Figure 8), but this was done by intermolecular cyclization.[15] For the purpose of an intramolecular cyclization, 1,3-bis-

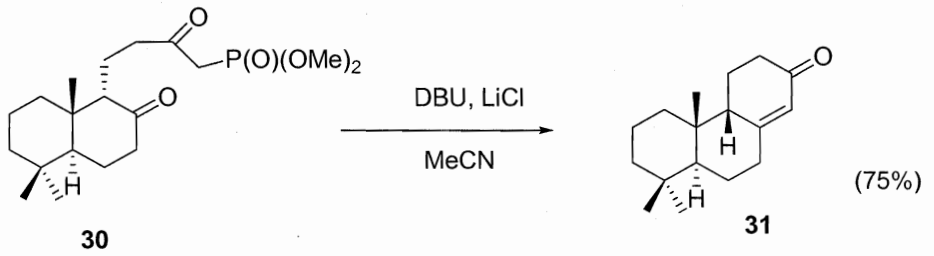


Figure 7. Heissler's cyclization of the tricyclic core using a HWE condensation.

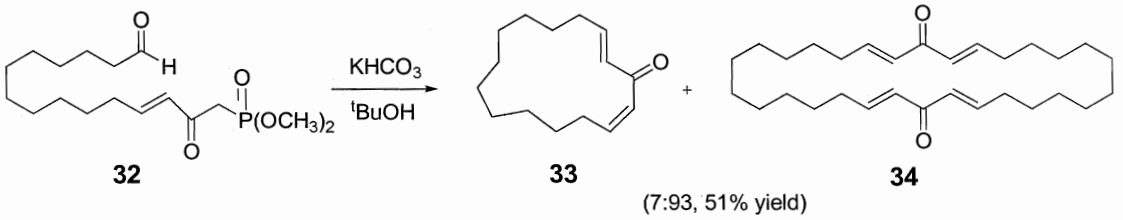


Figure 8. Cyclization of macrocycles utilizing a HWE condensation reaction.

(diethylphosphono)-2-propanone **35** will be used as the phosphonate species. With the use of bisphosphonate **35** comes the concern that the HWE reaction would result in not only the desired monocondensate **36**, but also the unwanted dicondensate **37** (Figure 9) by condensation on both sides of the bisphosphonate **35**. A model reaction is needed to explore the possibility of a monocondensation reaction of bisphosphonate **35**.

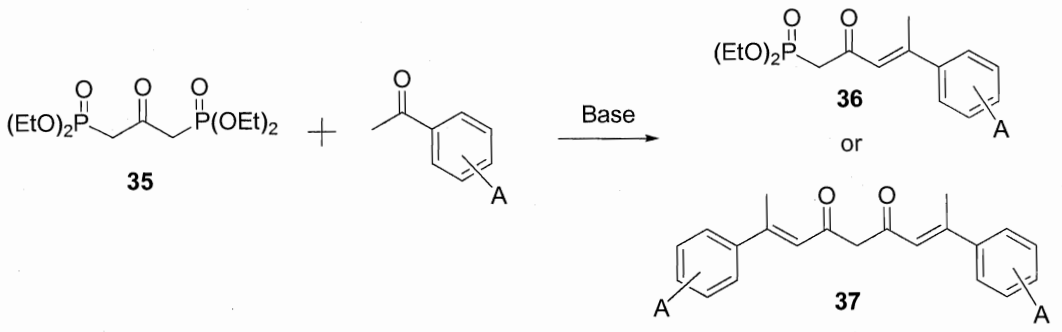
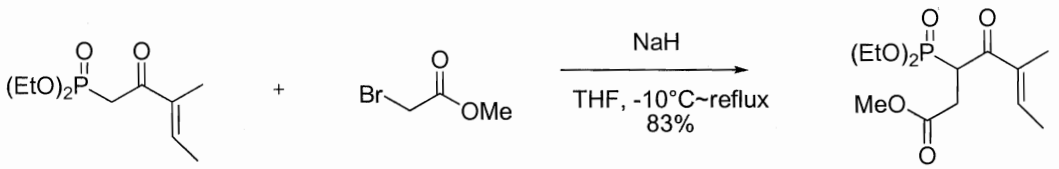


Figure 9. Possible products for condensation of bisphosphonate **35** with a carbonyl species.

The second type of phosphonate reaction required in this study is an S_N2 type substitution. Phosphonates resemble carbonyl species, with fairly acidic α-protons that can easily be deprotonated to give a nucleophilic species for a S_N2 reaction and result in the formation of C-C single bond. The phosphonate substitution is crucial as it was required to convert decalin **27** into tricyclic core **26** in the retrosynthetic scheme. Contrary to the HWE reaction, the substitution reaction would retain the phosphonyl portion for further modifications. Several literature articles[16,17] have reported phosphonate substitutions, for example Mikolajczyk's group treated phosphonate **38** with bromoacetate under basic conditions (Figure 10) to give the substituted compound **40** in high yield. However, most phosphonate substitution reactions reported employ primary or secondary acyclic leaving groups, whereas substitutions on a secondary leaving group on cyclic systems are not yet clear. In this synthesis of stellettins, the decalin precursor **27** will be cyclized by a substitution reaction of a cyclohexyl leaving group, and therefore this step required model reactions to study first.



38 **39** **40**

Figure 10. Mikolajczyk's nucleophilic substitution of phosphonate on bromoacetate (**39**).

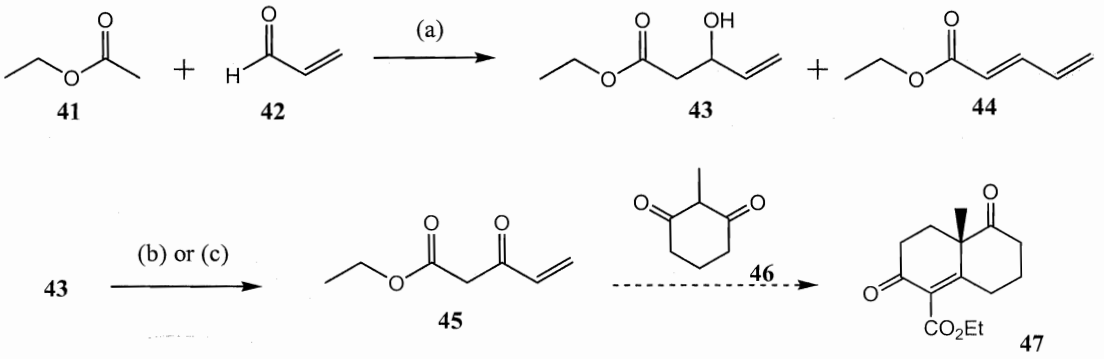
Both condensation and substitution reactions occur in basic environments. Therefore for the reaction of bisphosphonate **35** with decalin **27**, it was not certain which reaction would dominate. Nevertheless, in order to install the C-ring to the decalin ring, both condensation and substitution reactions are needed in the synthetic route (**28**→**26**). In this research, the synthetic goal is divided into two parts. The first part consists of formation

of the decalin core, and the second part involves model reactions for studying HWE reactions and substitution reactions.

Results & Discussion

Chapter 1 – Decalin Synthesis

To synthesize the stellettins, the first approach to synthesize the required decalin **47** (Figure 11) was from β-ketoester **45** and 2-methyl-1,3-cyclohexanedione **46**. Under basic conditions, both a Michael addition and an Aldol reaction occur to give the Robinson annulation product.[18] Decalin **47** has the advantage of having functionality at C-4, which can be modified as required for the C-19 oxidation pattern of various stellettins or stelliferins.



(a) LDA, THF at reflux (35%); (b) Pyridinium dichromate, 4Å molecular sieve at rt.;

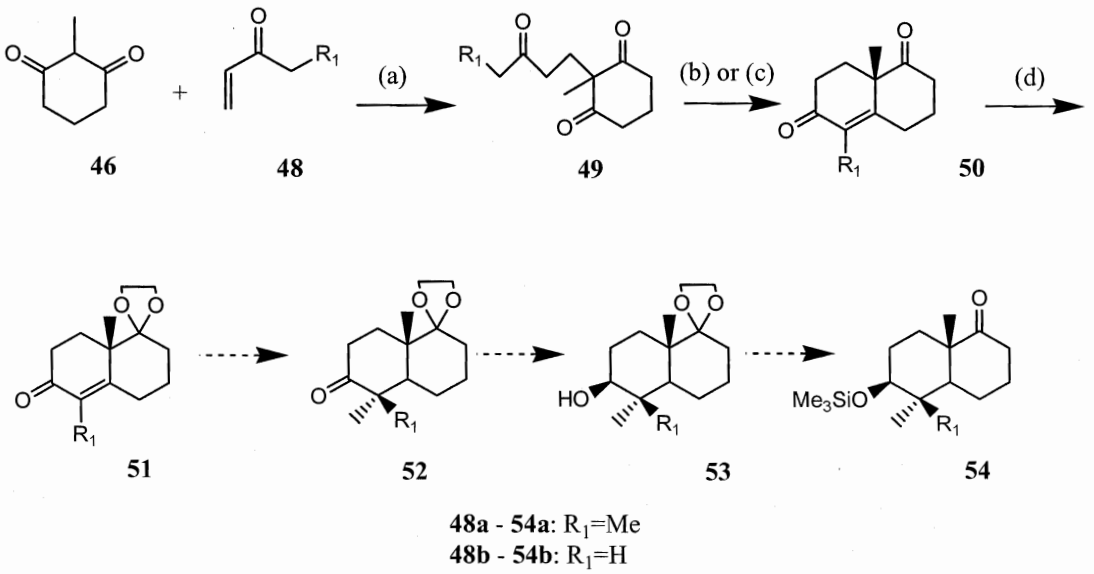
(c) MnO_2, CH_2Cl_2 (91% crude).

Figure 11. Ethyl acetate pathway to prepare decalin **19** for synthesis of stellettin.

The first step involved reacting the enolate of ethyl acetate **41** with acrolein **42** in an Aldol fashion[19] to afford hydroxy ester **43**. The initial attempt to synthesize this alcohol afforded only the elimination product of a conjugated diene, compound **44** (38%). ^1H NMR spectroscopy revealed a second set of vinylic hydrogens at 7 ppm, instead of the expected allylic hydrogen peak at 4 ppm. This elimination was caused by having a HCl

wash in the workup stage to neutralize the base, but it also acid catalyzed the elimination. By not using the HCl wash, hydroxyl ester **43** was obtained (35% yield), as evidences by the 4.55 ppm multiplet representing the allylic alkene and presence of two doublet of doublets for the α-carbonyl protons. Hydroxyl ester **43** then underwent oxidation to form β-ketoester **45**, the precursor to carboxy substituted decalin **47**. Initially pyridinium dichromate over molecular sieves was used as the oxidant[20] (Method B), but no product was obtained after purification using column silica gel. This method was then tested in the oxidation of benzhydrol and a 100% yield was obtained. Since this method proved satisfactory for the oxidation of comparable compounds, the failure to form β-ketoester **45** was likely not successful due to the loss in the purification process. So oxidation using manganese(IV) oxide[21] (Method C) was next tried, and this method afforded as much as 91% of the crude product. But unfortunately due to repeated experiments at the oxidation step, not enough material was left for the next reaction, and alternative methods of the decalin synthesis were explored.

The second strategy utilized the Wieland-Miescher ketone (Figure 12) as the decalin core. Commercially available 2-methyl-1,3-cyclohexanedione (**46**) was treated with ethyl vinyl ketone (**48a**) to yield triketone **49a** as a thick, light yellow oil (64.1%).[22] The same reaction was carried out using methyl vinyl ketone (**48b**) to afford triketone **49b** (54.8%). The crude oils were purified by vacuum distillation, and ^{1}H NMR spectra confirmed the identity of the products, as both spectra showed a sharp 3H singlet at 1.2 ppm for the 2-methyl substituent. The difference in these spectra was triketone **49b** had a singlet for α-carbonyl, while the α-carbonyl protons in triketone **49a** were split by the terminal methyl into a quartet. In addition, no vinylic hydrogens (4.5-6.5 ppm) were observed in the spectra. The identity of triketone **49b** was confirmed by ^{13}C spectroscopy with two peaks after 200 ppm for the two types of carbonyl carbons.



48a - 54a: R_1=Me
48b - 54b: R_1=H

(a) KOH, MeOH at reflux. (**49a**: 64.1%, **49b**: 54.8%).; (b) L-PheAla, D-CSA, DMF, 30-70°C in 4 days. (**50a**: 22.7%, **50b**: 25.9%); (c) L-PheAla, HOAc at reflux. (**50a**:75.4%, **50b**: 52.0%); (d) Ethylene glycol, p-TsOH, toluene at reflux (**51a**: 56.6%, **52b**:31.0%).

Figure 12. Vinyl ketone pathways to synthesize and modified Wieland-Miescher ketone.

The next reaction sought to stereoselectively close the second ring to yield the Wieland-Miescher ketone using L-phenylalanine in an acidic environment. The first method attempted used D-camphorsulfonic acid,[23] but perhaps due to improper control of the temperature, the yield of decalins **50a** and **50b** were unacceptably low (**50a**: 22.7%; **50b**: 25.9%). Additionally, a large amount of unreacted starting materials were recovered. Therefore, this reaction was attempted again using acetic acid as the acid source[24] instead of D-camphorsulfonic acid. The yield for crude product was significantly higher (**50a**: 64.1%, **50b**: 54.8%) by this method. ^{1}H NMR spectroscopy confirmed an allylic methyl peak at 1.82 ppm. The ethyl vinyl ketone derived decalin **50a** was purified via vacuum distillation without any problem. However, the methyl vinyl ketone derivative decalin **50b** is a solid at room temperature, so purification by other methods was necessary. Although some crystals were successfully obtained from decalin **50b**, the yield was still

really low (2.3%). The first attempt at crystallization involved dissolving the crude product in boiling hexanes, allowing the solution to cool to room temperature, and storing it in the freezer. However, most of the time the solution turned back to an orange oil and no crystals formed. It could be that the unwanted byproducts present in the crude product affected the crystallization of the pure compound. The second attempt at purification used dry column chromatography with 30g silica gel, and collecting 15mL fractions. TLC analysis of the resulting fractions suggested that the crude product was not purified at all. Therefore, column chromatography was used to successfully obtain purified decalin **50b** (31.0%).

With pure decalin **50a** and **50b** derived from the vinyl ketones, the acetal reaction[19] went quite nicely, as ^{1}H NMR spectra contained a peak at 4 ppm, corresponding to the acetal group. However, only less than 300mg of decalins **51a** (56.6%) and **51b** (31.0%) were obtained. These reactions should be repeated in the future to produce more materials to continue along the proposed sequence. The next reactions involve stereoselective addition of methyl group at C-4, followed by reduction of the carbonyl group at C-3 to an alcohol. Finally, the acetal at C-9 would be removed and a protecting group at C-3 would be installed.

Overall, following the three literature routes to prepare the decalin cores for synthesis of stellettins provided the desired compounds in low yields, which significantly limited the amount of material available to perform the further reactions. The cumulative yield for acetal **51a** was 29.1% over 3 steps; acetal **51b** was 14.0% over 3 steps; and diketone **45** was 34.8% over 2 steps. These reactions should each be optimized such as better purification for each step to maximize the yield and purity in order to proceed along in the sequence.

Chapter 2 – Studies of the C-Ring Closure with Phosphonates

One of the main challenges for the synthesis of the stellettins is to close the C-ring, which corresponds to the 5-member ring in the tricyclic core. There are several strategies in the literature for synthesis of a 6,5-bicylic ring system, such as pericyclic reactions,[25] biomimetic cascade cyclizations from polyene,[26] and acid-catalyzed exocyclic ring closure from an aldehyde and alkene.[27] In this research, phosphonate chemistry was selected to perform this task. The main advantage of the phosphonate chemistry approach is that after the ring closure, there is still a phosphonyl at the C-13 position that is convenient for adding the side chain addition by Horner-Wadsworth-Emmons (HWE) chemistry.

Since the decalin core precursor was difficult to produce in large quantities, a model reaction was used to test the ring closure reaction with tosylated cyclohexanone **56** (Figure 13). *p*-Toluenesulfonic acid has a very low pKa value, and therefore the tosylate is a weak base and is preferred in ionic form, making it an excellent leaving group. When tosylate **56** is treated with 1,3-bis-(diethylphosphono)-2-propanone **35** under basic conditions, a S_N2 nucleophilic attack of the phosphonate anion on the tosylate could form a C-C bond (route A in Figure 13) to give cyclohexanone **57**, which could then be cyclized into the bicyclic core **58** by a HWE reaction. On the other hand, this Wittig-type condensation might occur before the nucleophilic substitution (route B) which would result in the formation of an exocyclic bond (enone **59** and **60**). In this case, if the substituents on the cyclohexanone ring do not have any steric effects, racemic *cis*- and *trans*- isomers would be obtained. Due to the rigidity of the olefin, only the *cis*-isomer would be able to undergo cyclization to indanone **58**. If the *trans*- isomer was produced, reduction of the double bond to a single bond would be necessary to remove the rigidity

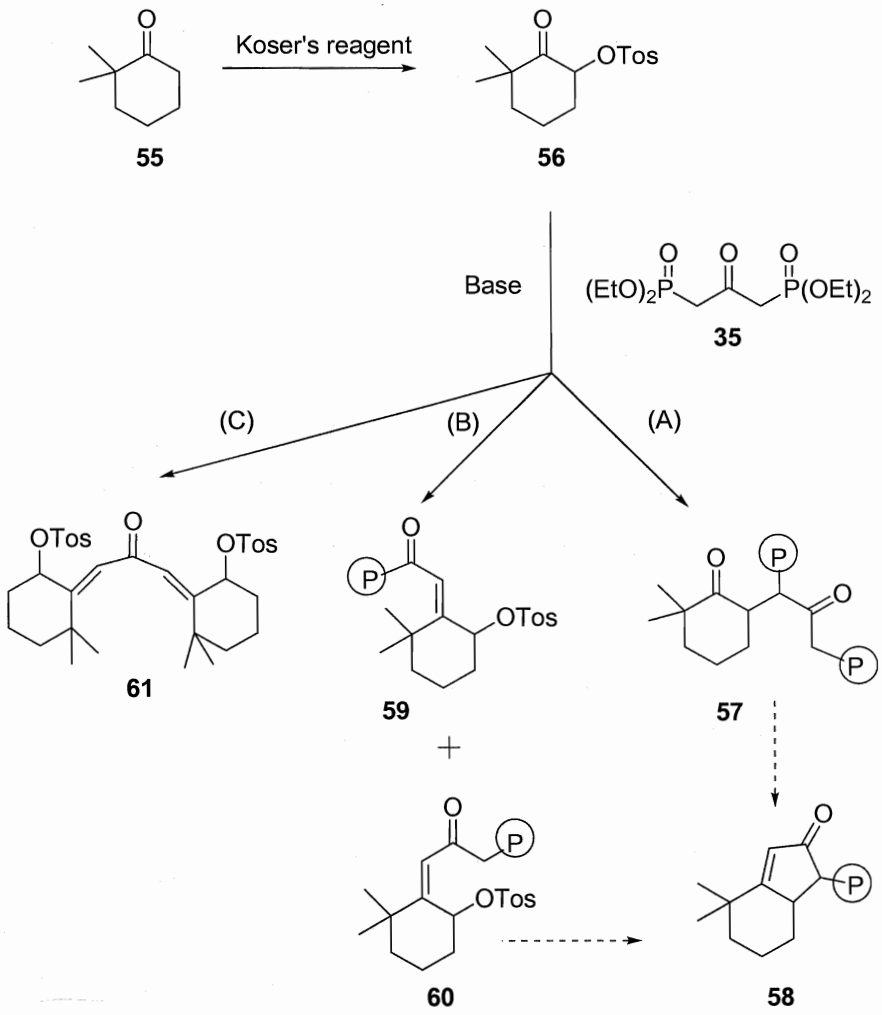


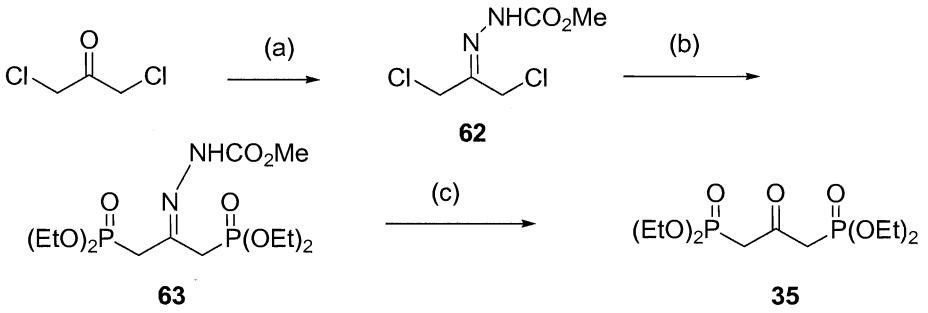
Figure 13. Possible routes for the C-ring cyclization reaction to give (A) nucleophilic substitution, (B) monocondensation or (C) dicondensation.

and allow the cyclization. In addition, this reduction might also be needed for the *cis*-isomer if the double bond is too rigid to allow the nucleophile to attack the tosylate. Therefore, route B may require one additional step after reaction with the bisphosphonate and prior to the ring closure. Both routes should therefore give the hydrindanone regardless of which chemistry occurred first.

Condensation Reaction of Bisphosphonate 35

The HWE condensation reaction of bisphosphonate **35** is a key part of this synthetic scheme (**56→59(60)**, **57→58**). The main challenge with the use of this phosphonate is the possibility of the reaction giving the dicondensate product (route C). That is, one molecule of bisphosphonate **35** could react with two equivalents of the carbonyl compound, forming the dicondensation product **61**. One method to ensure monocondensation would treat the phosphonate with NaH and n-BuLi. The first base (NaH) would deprotonate the phosphonate, followed by a second deprotonation by the stronger base (*n*-BuLi) to form a dianionic species.[28,29] Since the dianionic bisphosphonate is much more reactive than anionic species, and only one equivalent of aldehyde is treated with the bisphosphonate **35**, it is expected only the monocondensate product will be formed, but the order of the base addition was crucial in this reaction. Further more, if only one equivalent of the base is used, solely the dicondensation product will be formed even if it is treated with one equivalent of aldehydes.

Bisphosphonate **35** was produced by a known three-step synthesis (Figure 14).[30] 1,3-Dichloroacetone was treated with methyl hydrazinocarboxylate by nucleophilic addition to the carbonyl to give compound **62** (73% yield), with the protecting group preventing the elimination by the triethyl phosphite in the next reaction. With the hydrazone protecting group in place, the phosphite substituted for the two chloride leaving groups to give bisphosphonate **63** (59% yield), and acidic hydrolysis removed the hydrazone group. After column chromatography in the last step (95:5 CH_2Cl_2:MeOH), pure bisphosphonate **35** (15% yield) was collected for the condensation reactions. The low yield was probably due to the loss in the final purification step.



(a) H_2NNHCO_2Me, EtOH (73%); (b) $P(OEt)_3$, toluene (59%);

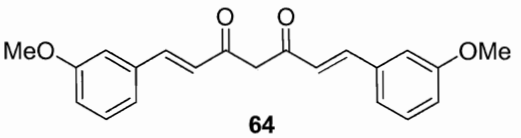
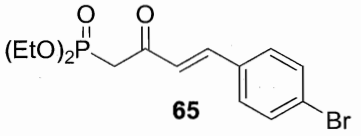
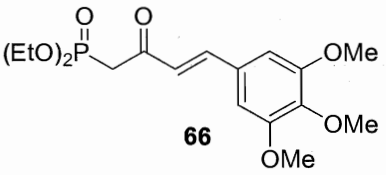
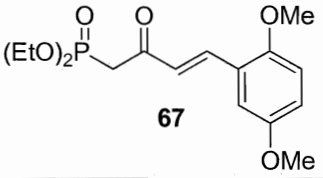
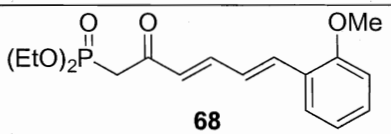
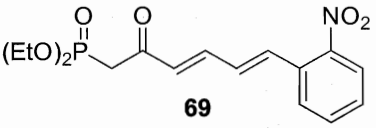
(c) 3M HCl, H_2O, acetone (15%)

Figure 14. The synthesis of bisphosphonate **35**.

To test the selective monocondensation, reactions of bisphosphonate **35** with various aldehydes were performed and the products were analyzed by ^{1}H NMR spectroscopy (Table 1). Aldehydes were chosen as the carbonyl species since they are more reactive than ketones. In addition, benzaldehydes and cinnamaldehydes were lack an acidic α-carbonyl proton, and hence prevent quenching of the phosphonate anions, or leading to Aldol side reactions to give byproducts.[31]

Most of the aldehydes yielded the desired monocondensation product in a 30~73% yield. The products were identified in the ^{1}H NMR spectra by the presence of phenyl protons at 7~8 ppm, corresponding to the aldehyde portion; a phosphorus coupled doublet of 22.6Hz at 3.3ppm, representing the α hydrogens of the phosphonate portion; as well as new vinyl proton peaks at 6.5-7.3 ppm. Each monocondensation product revealed doublets at 6.7~7.1 ppm with 15~17Hz coupling constants, corresponding to the *trans*-olefinic protons since *cis*- protons generally have J = 6~12Hz. Therefore, the ^{1}H NMR spectra suggested exclusive formation of *E*-olefin linkage, instead of the *Z*-configuration. The reaction using *m*-anisaldehyde gave only the dicondensation product **64**, as the ^{1}H NMR spectrum lacked the α-phosphonate doublet and ethyl signals. This

Table 1. The aldehydes used for monocondensation reactions.

Entry	Aldehyde	Product[a]	Yield
1	*m*-anisaldehyde	 **64**	84.2%[b]
2	*p*-bromo-benzaldehyde	 **65**	30.7%
3	3,4,5,-trimethoxy-benzaldehyde	 **66**	47.1%
4	2,5-dimethoxy-benzaldehyde	 **67**	37.9%
5	2,3-dimethoxy-benzaldehyde	NONE	N/A
6	*o*-methoxy-cinnamaldehyde	 **68**	73.5%
7	*o*-nitro-cinnamaldehyde	 **69**	66.7%

Note: [a] Each reaction was performed by treating bisphosphonate **35** (1.0 equiv) in THF, then treating with NaH (1.2 equiv) and *n*-BuLi (1.04 equiv) at 0°C, followed by the addition of the aldehyde component (1.06 equiv). [b] Dicondensate yield was calculated by considering *m*-anisaldehyde as the limiting reagent.

was possibly due to improper control of the base addition. The other unsuccessful reaction used 2,3-dimethoxybenzaldehyde, which did not seem to react at all. When this

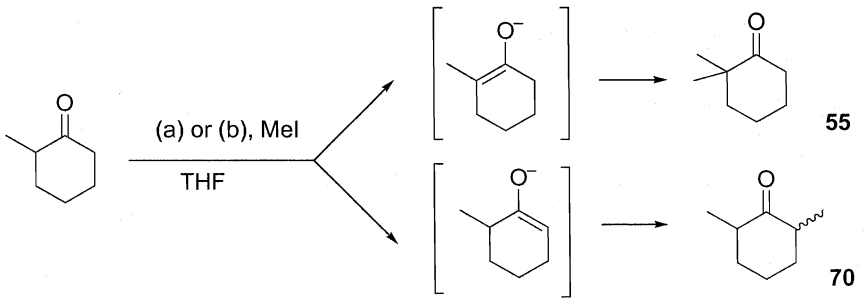
reaction was performed, the bisphosphonate solution was unusually orange instead of the usual pale yellow. Therefore, it was possible that the bisphosphonate was quenched by atmospheric moisture prior to the reaction with aldehyde, and hence the reaction did not occur. These results suggested that the monocondensation of bisphosphonate **35** was achievable and could be applied to the third ring synthesis.

Methylation of 2-methylcyclohexanone

In order to test the phosphonate condensation and substitution reactions with cyclohexanones for cyclization studies (Figure 13), the first step was to prepare a cyclohexanone with one fully substituted α-carbonyl site, so the leaving group can be installed regioselectively, and also preventing enolization on the other side of the carbonyl for side reactions. α-Tetralone was initially selected as the substrate for the phosphonate reactions due to its structural similarity to the decalin core and its commercial availability. However, when the tosylation of α-tetralone was performed, it was too reactive and produced various byproducts as suggested by TLC analysis. Therefore, 2,2-dimethylcyclohexanone **55** was used as the model substrate.

The one-step synthesis of 2,2-dimethylcyclohexanone from 2-methylcyclohexanone was somewhat challenging, since the byproducts, such as 2,6-dimethylcyclohexanone or other polysubstituted cyclohexanones, were difficult to differentiate on the TLC plate. Since byproducts were produced, the overall yield of the desired product **55** was low. The first method attempted for the methylation of 2-methylcyclohexanone used potassium hydride as the base (Method A).[32] The hydride would deprotonate cyclohexanone to give the enolate, which then S_N2 attacked MeI to add the methyl group. Depending on the reaction conditions such as temperature and reaction time, two different enolates could be produced that have different energy states and reaction rates

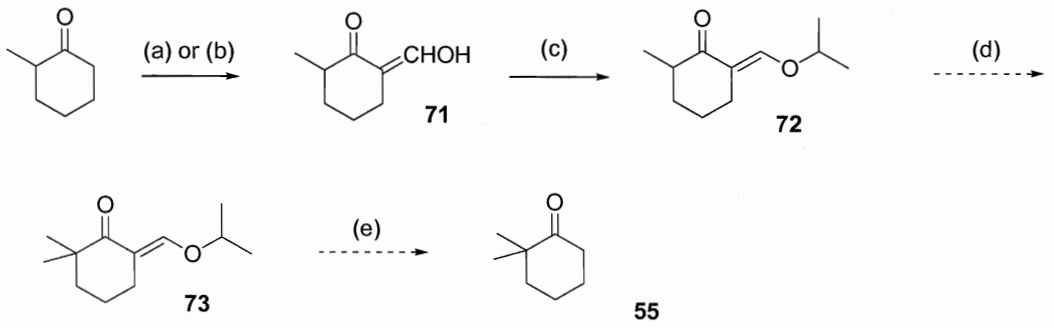
(Figure 15). The 2-methyl enolate (the thermodynamic enolate) would give the 2,2-dimethyl product **55**, while the 6-methyl enolate (the kinetic enolate) would lead to the formation of 2,6-dimethyl product **70**. This 2,6-dimethyl product **(70)** would be diastereomeric since the transition state of the kinetic enolate did not suggest much of a preference for nucleophilic attack on either face of the enolate. The 2-methyl substituent on the enolate is too small to have a significant steric effect on the stereoselectivity. In order to solely produce the 2,2-dimethyl product, the formation of thermodynamic enolate should be formed over the kinetic enolate using thermodynamic control, and the reaction should be run at higher temperatures and longer reaction times.[33] After the reaction was performed and purified by vacuum distillation, the product ^{1}H NMR spectrum revealed several large singlets and doublets in the methyl region, corresponding to various CH_3 substituents and suggesting the presence of byproducts and starting material. The reaction was reattempted, switching to a less powerful base of potassium hydroxide (Method B), allowing an equilibrium to be established between the two enolates, and conversion to the thermodynamic enolate over time. Monitoring of the reaction by gas chromatography suggested about a 1:1.2 starting material:product ratio, and the product was hard to separate from the starting material unless very accurate solvent system was used for chromatography. The direct methylation of 2-methylcyclohexanone was difficult so an alternative method was used.[34]



(a) KH, Et_3B, THF, rt, 1 day, 38% yield; (b) KOH, DME, rt, 1 day, 37% yield.

Figure 15. Direct methylation of 2-methylcyclohexanone.

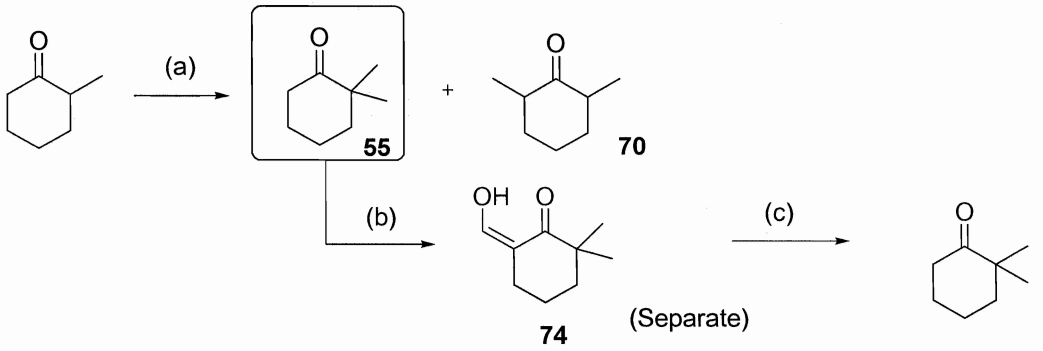
The next attempt (Method C) involved blocking the formation of kinetic enolate before the methylation[35] (Figure 16). This strategy involved attachment of an olefin at C-6 of 2-methylcyclohexanone so that only the thermodynamic enolate could form, and thus 2-methylcyclohexanone was treated with ethyl formate in an Aldol reaction. The cyclohexanone enolate attacked the ester carbonyl to make the first C-C bond, and the ethoxy portion was cleaved to form an aldehyde, which tautomerized to hydroxymethylene **71**. Originally metallic sodium was used as the base, but later studies showed NaH gave much better results in terms of purity and yield (from 4.6% to 121% yield of crude product). To enhance the steric bulk of the protecting group and to prevent the consumption of the base by the alcohol in the next step, hydroxymethylene **71** was treated with a weak base to deprotonate the alcohol, and a S_N2 reaction with 2-bromopropane formed isopropoxymethylene **72** (53.6%). With one side of the carbonyl fully protected, the methylation reaction with MeI was carried out, similar in manner to the previous methylations to give 91.5% of the crude product. Acidic hydrolysis would then deprotect the isopropoxymethylene group and give final product **55**. At first, this series of reactions were carried out without any purification or characterization of the intermediates (**71**~**55**), but the overall result by TLC of the final reaction showed the presence of many byproducts. Thus the reactions were carried out stepwise with ^{1}H NMR spectra of the intermediates taken at each step. The ^{1}H NMR spectrum suggested hydroxymethylene **71** was successfully obtained, since a new vinylic proton peak at 8.61 ppm and an enol peak at 14.58 ppm were observed. ^{1}H NMR spectroscopy suggested isopropoxymethylene **72** was also obtained due the disappearance of the enol peak and a new CH ester multiplet at 4.19ppm. However, the spectrum collected for the product of the methylation step revealed the absence of the isopropyl ester peaks, suggesting that the protecting group fell off in this step. Many byproducts were observed by TLC that were deemed too difficult to separate efficiently.



(a) Na, MeOH, ethyl formate (4.6%); (b) NaH, MeOH, ethyl formate (121%); (c) 2-bromopropane, K_2CO_3 (53.6%); (d) K_2CO_3, MeI (91.5%); (e) MeOH, dilute HCl

Figure 16. Synthesis of 2,2-dimethylcyclohexanone by protecting group strategy (Method C).

Another possible way (Method D, Figure 17) to synthesize 2,2-dimethyl-cyclohexanone was a combination of Method A and Method C approach in that the 2,2-dimethyl product **55** would be separated out from the 2,6-dimethylated byproduct **70** in a heterogeneous mixture.[36] The strategy involved converting the 2,2-dimethyl product to a hydroxymethylene moiety similar to alcohol **71**, which would make it very water soluble while the 2,6-dimethyl products, lacking a secondary α-carbonyl site, could not form a hydroxymethylene group. Since the later compound would not be water soluble, a simple extraction would easily separate the two compounds. In the reaction, 2-methylcyclohexanone was treated with iodomethane and sodium amide in ether. After three hours of reflux with careful monitoring of the reaction by GC (GC: Initial temp: 100°C, rate: 0.1°C/min), 85% of 2,2-dimethylcyclohexanone was present with only 15% of the 2,6-dimethylated byproduct and no unreacted starting material. After work up of the reaction, the product identity was confirmed by ^{1}H NMR spectroscopy and considered pure enough for next reaction without requiring preparation or separation of the hydroxymethylene derivative.



(a) $NaNH_2$, MeI, Ether, 3 hr reflux (73% yield, 85:15 **55**: **70**);

(b) NaH, ethyl formate, MeOH; (c) dilute HCl

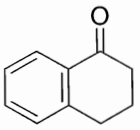
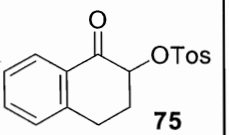
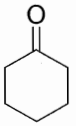
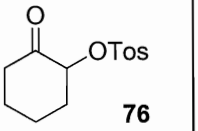
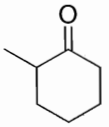
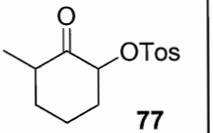
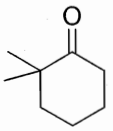
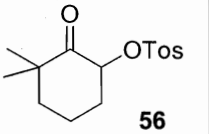
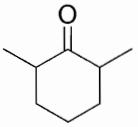
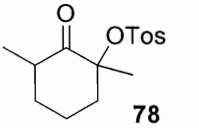
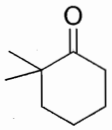
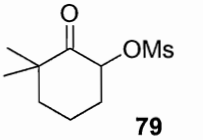
Figure 17. Alternative strategy to synthesize 2,2-dimethylcyclohexanone by separation.

Tosylation of Carbonyls

With 2,2-dimethylcyclohexanone of acceptable purity in hand, the next reaction involved the tosylation of these carbonyl species as well as related carbonyl compounds. The tosylation method chosen used [hydroxy(tosyloxy)iodo]benzene (Koser's reagent)[37] as the tosylating agent since it was easier to prepare and no purification of the products was needed. Koser's reagent was prepared by treating iodobenzene diacetate with *p*-toluenesulfonic acid monohydrate. A colorless precipitate formed immediately at room temperature and it was collected by vacuum filtration (78% yield). A melting point of 135~138°C was obtained and matched the literature value of 135~138°C.[37]

Tosylation of α-tetralone was first tested (Table 2) by treating α-tetralone with Koser's reagent in dry acetonitrile.[38] After the reaction was worked-up, the ^{1}H NMR spectrum revealed a large amount of byproducts, suggesting that the α-tetralone was too reactive and there were too many competing side reactions occurring.

Table 2. Tosylation and mesylation of cyclohexanone derivatives.

Substrate	Product	Conditions	Yield
	 **75**	1 day reflux	0% Too reactive
	 **76**	2 day rt 10 min reflux	47%
	 **77**	2 hr rt	16% 1:1.03 *trans* : *cis*
	 **56**	2.5 hr rt	35%
	 **78**	1 day reflux	0% No reaction
	 **79**	2 days rt	49%

Therefore, simple cyclohexanones were used as substrates for the tosylation reaction. These reactions went well (35~47% yield) with a short reflux time. TLC analysis suggested small amounts of starting material remained after the reaction, but instead of performing time consuming column chromatography, treating the crude product with hexanes was used as a much faster and less expensive way of purification. Since the tosylcyclohexanones were insoluble in hexanes, repeated additions of small portions of

hexanes (2mL) would wash away the cyclohexanone starting material, leaving the product as an oil in the bottom of the flask. Once the trace amounts of hexanes were removed on the vacuum pump, square crystals of the final products were obtained. The product with cyclohexanone was shown by ^{1}H NMR spectroscopy to contain two clear doublets at 7.3 and 7.8 ppm for the phenyl portion of the tosylate, and a 1H doublet of doublets at 4.9ppm, suggesting tosylation occurred at α-carbonyl site. There were no other unexpected peaks in the ^{1}H NMR spectrum, suggesting tosylate **76** had very good purity.

Other cyclohexanone derivatives were also tested with Koser's reagent. Tosylation of 2-methylcyclohexanone gave tosylate **77** as a yellow oil, appearing as two spots by TLC (R_f = 0.40, 0.51 Hexanes:EtOAc 7:3). After separation by column chromatography (Hexanes:EtOAc 72:28), the ^{1}H and ^{13}C NMR spectra of the two product suggested that they were *cis*- and *trans*- diastereomers. Since current literature only reported the racemic ^{1}H NMR spectrum,[39] there was no direct mapping to the reported spectra for diastereomer assignments. The compound with the higher ^{13}C NMR shift was assigned as the *trans*-tosylate, because the 6-methyl substituent could shield the electron density of *cis*-tosylate through space. The diastereomer with the lower chemical shifts was assigned to the *cis*-tosylate. On the other hand, the ^{1}H NMR spectra showed very close chemical shifts of the two diastereomers, making it difficult to distinguish the stereoisomers.

With successful model tosylation reactions, the 85:15 2,2-dimethylcyclohexanone : 2,6-dimethylcyclohexanone mixture from the previous experiment was treated with Koser's reagent. The solid product characterized by ^{1}H NMR spectroscopy suggested formation of pure 2,2-dimethyltosylate **56** in a 35% yield. The possible byproduct of 2,6-dimethyltosylate **78** was not observed, as no doublet CH_3 signals were present in the

^{1}H NMR spectrum. Based on this observation, it was hypothesized that Koser's tosylation reaction may occur only at primary and secondary α-carbonyl sites. The tertiary site may be too sterically hindered for tosylation to occur, and no successful α-tosylations of cyclohexanones at tertiary sites via Koser's reaction have been reported. This makes it hugely advantageous that the 2,2-dimethylcyclohexanone is not required to be very pure before tosylation, as the 2,6-dimethyl byproduct does not react with Koser's reagent.

To test this assumption about tertiary sites, commercially available 2,6-dimethylcyclohexanone was subjected to tosylation. After refluxing the reaction mixture overnight, TLC showed only the presence of unreacted starting material. Thus Koser's tosylation does not work at tertiary α-carbonyls site, or at least not as readily as with 1° or 2° substrates.

Additionally, the mesylate of 2,2-dimethylcyclohexanone was made in a 49% yield by a similar procedure as in tosylate reaction, using [hydroxy(mesyloxy)iodo]benzene. ^{1}H NMR spectroscopy of the final product revealed the presence of mesylate methyl peak at 3.21ppm, confirming the mesylate product **79** was obtained.

Nucleophilic Substitution of Phosphonate

With tosylated cyclohexanone derivatives prepared, the attachment of the phosphonate group onto the cyclohexanone ring could be studied. These reactions involved treating the tosylate compounds with the phosphonate and a base. This is the key reaction of the entire scheme, because the chemistry of using a phosphonate as a nucleophile on a cyclohexyl system was not yet reported in organic synthesis. A model reaction was developed to test this chemistry since formation of tosylate **76** or **56** required a large amount of Koser's reagent (for example, 0.15mL of cyclohexanone

required as much as 0.62g of Koser's reagent to give at most 0.38g of product if 100% yield obtained). Cyclohexyl tosylate was selected as the model substrate. Cyclohexanol was treated with anhydrous *p*-toluenesulfonyl chloride in pyridine at 0°C to give a yellow oil which crystallized at -78°C, affording white needles of pure cyclohexyl tosylate[40] (Figure 18, 75% yield). This reaction was fast to perform and used a less expensive reagent, so that a large amount of cyclohexyl tosylate was prepared to study the phosphonate reaction. However, because this model lacked the carbonyl group, a condensation of the phosphonate would not be observed in this model. Nevertheless, this model should be sufficient to test the ability of a nucleophilic substitution of a phosphonate to occur on a cyclic tosylate compound.

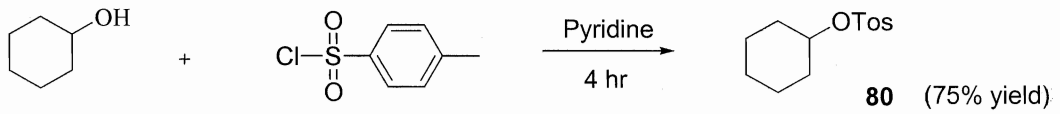


Figure 18. Synthesis of cyclohexyltosylate.

The phosphonate substitutions (Figure 13, **56→57**) using strong bases were highly air sensitive, therefore any trace amount of water would completely destroy the reaction by consuming the base. Also, in order to prevent a competing E2 elimination of the tosylate, the order of the addition was crucial. In this reaction, the phosphonate was first deprotonated by the base, and the solution stirred for at least 30 minutes at reflux to allow all of the base to be consumed. The tosylate solution was then added via cannulae to prevent exposure to air. If TLC analysis of the reaction suggested no progress, it was then heated to reflux for a maximum of five days (Table 3).

Table 3. Study of nucleophilic substitution reactions.

Entry	Substrate	Nucleophile	Base	Solvent	Result
1	cyclohexyl tosylate (**80**)	$(MeO)_2P(O)CH_2CO_2Me$	imidazole	MeOH	No rxn
2	"	"	pyrrole	MeOH	No rxn
3	"	"	Na	MeOH	No rxn
4	"	"	NaH	THF	No rxn
5	"	"	LiCl/DBU 15-crown-5	THF	No rxn
6	"	$(EtO)_2P(O)CH_2CO_2Et$	NaH	DMF	cpd **81** (37%)
7	"	"	NaHMDS	DMF	cpd **81**
8	"	"	KH HMPA	DMF	No rxn
9	"	"	MeLi HMPA	DMF	No rxn
10	"	"	LiCl/DBU 15-crown-5	DMF	No rxn
11	"	"	NaH	DME	No rxn
12	"	"	nBuLi	DME	No rxn
13	"	EtOAc	NaH	DME	No rxn
14	"	pentan-1-amine	-	DME	No rxn
15	benzyl bromide	$(EtO)_2P(O)CH_2CO_2Et$	NaH 15-crown-5	DMF	cpd **82** (15%)
16	"	"	NaH	THF	cpd **82**
17	2-chloro-cyclohexanone	"	NaH	THF	cpd **83** (48%)
18	"	"	NaH	DME	cpd **83**
19	"	EtOAc	NaH	DME	No rxn
20	6,6-dimethyl-2-mesyl-cyclohexanone (**79**)	$(EtO)_2P(O)CH_2CO_2Et$	NaH	DME	cpd **84** (41%)

The phosphonate reaction with cyclohexyl tosylate (entries 1-12, Table 3) was carried out using different bases, such as hydrides, amines, or metallic alkalis to deprotonate phosphonate with a pKa of 12.2.[41] The lack of reaction was evident in the ^{1}H NMR spectrum by the presence of two sets of doublets at 7.3 and 7.8 ppm for the tosylate portion, and the absence of phosphonate ethyl multiplets at 4.2 ppm. The amine base was generally too weak to deprotonate the phosphonate, and thus these reactions did not occur. When lithium (LiCl with DBU, MeLi or *n*-BuLi), or sodium (NaH or metallic Na) bases were used, there was still no reaction for most cases except entries 6 and 7. The lithium cation can coordinate with the phosphonate anion, and to assist the metal coordination at times one drop of 15-crown-5 was added. Unfortunately the phosphonate was perhaps too hindered so that reaction did not occur. Variation of solvent did not help much in this case, as either THF, DMF or DME afforded the substituted product. Since the enolate of the phosphonate was less soluble in DME and gave a milky-white colored solution, several drops of HMPA were introduced into the mixture to enhance the solvent solubility. This treatment did not work either, implying the solubility of the phosphonate does not hugely affect the reaction. Surprisingly when using a sodium base in DMF, the reaction afforded an unexpected product in compound **81** (37% yield, Figure 19). The ^{1}H NMR spectrum revealed the absence of the ethyl ester portion of triethylphosphonoacetate, but showed a 1H multiplet at 4.8ppm, suggesting the ester oxygen was connected to the cyclohexyl group. This product occurred only when using NaH as the base in DMF. The mechanism for this reaction is not known, but the product is not the one desired. After several variations were attempted of this reaction, it was still unsuccessful in installing the phosphonate onto the cyclohexyl ring. Therefore, both starting materials were tested for their reactivity to identify the problem. The cyclohexyl tosylate was treated with other strong nucleophiles (pentan-1-amine and ethyl acetate, entry 13 and 14 respectively). Neither of the two reactions yielded any product, suggesting that the secondary tosylate

might be too sterically hindered to allow a nucleophilic reaction to occur. However, since there are literature reports of secondary tosylates were successfully substituted,[42] the cyclohexyl tosylate should be tested with other strong nucleophiles in the future.

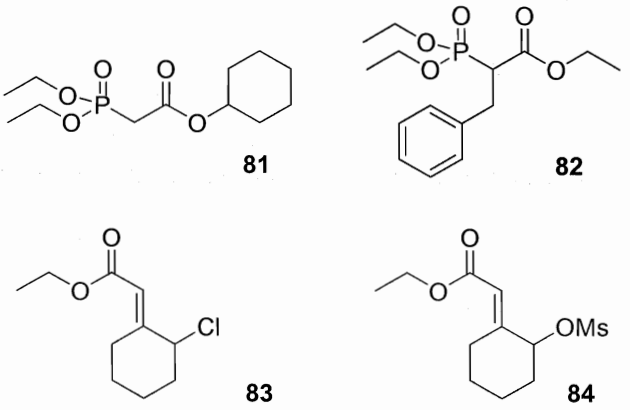


Figure 19. Products proposed from substitution reactions.

Another set of reactions was developed to test the nucleophilicity of the phosphonate. Benzyl bromide was selected as the substrate, since the primary leaving group (entries 15-16) is less sterically hindered. Because the reaction occurred by a S_N2 type mechanism, a primary leaving group should be most favorable. The reaction resulted in a successful attachment of the phosphonate to the benzyl group to give compound **82** (15% yield). The ^{1}H NMR spectrum showed the absence of α-phosphonate doublet at 3.0 ppm, but a presence of a multiplet at 3.4 ppm implying the linkage of the two portions. Both the phosphonate and phenyl regions could be clearly observed. Therefore, the phosphonate would undergo nucleophilic attack, at least with substrates bearing primary leaving groups.

In terms of α-halo cyclohexanones, 2-chlorocyclohexanone was used as the model substrate to explore this possibility (entries 17-19) and obtained as a brown oil was

compound **83** (48% yield). The ^{1}H NMR spectrum of this product showed the absence of α-phosphonate doublet at 3.0 ppm, and the proton next to the chloride group was moved slightly downfield. Most importantly, a vinylic singlet appeared at 5.9 ppm, suggesting the formation of 2-chlorocyclohexylidene acetate **83.** Therefore the reaction of phosphonate with 2-chlorocyclohexanone favored the HWE condensation over the substitution reaction.

Lastly, mesylated cyclohexanone, used in place of the tosylates, was used as the leaving group (entry 20), since secondary tosylate was believed to be too sterically hindered for nucleophilic attack. The product was obtained in 41% yield, and the ^{1}H NMR spectrum of mesylate **84** showed the disappearance of α-phosphonate doublet at 3.0 ppm, while a vinyl singlet was observed at 5.9 ppm, suggesting the condensation product was forming. The meyslate portion was still observed at 2.05 ppm, and the ethyl ester signals at 4.05 ppm revealed two equal quartets, implying the formation of both *E*- and *Z*- olefin from the condensation. ^{13}C NMR spectrum showed the absence of doublet at 20~60 ppm, confirming the product lacked a phosphonate group.

This evidence suggested that the HWE reaction took place rather than the substitution. Based on the model reactions of substitution, the bisphosphonate reaction on α-substituted cyclohexanone may give the HWE condensation product, suggesting B route (Figure 13) was more likely to occur than A route. However, due to unsuccessful substitution of phosphonate on cyclic secondary centers, the cylization step (**60→58**) may be difficult.

Conclusions

The core synthesis using both ethyl acetate and vinyl ketone pathways were successful, however the low yields were the concern that limits the amount of material for further reactions. Tosylation of α-carbonyl by Koser's reagent suggested possible primary or secondary α-carbonyl tosylation, whereas tertiary centers such as 2,6-dimethylcyclohexanone was too sterically hindered. With the correct conditions, HWE conditions of 1,3-bisphosphonate could achieved solely the monocondensate products. Phosphonate nucleophilic substitution at cyclic secondary centers appeared to be difficult, as tosylate leaving group may be too sterically hindered to allow substitution to occur, while chloride and mesyl leaving groups gave condensation product. It suggested a possible installation of the bisphosphonate onto the decalin core, however the cyclization step involving substitution on cyclic secondary center may be difficult to occur.

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Experimental

General Techniques All reagents were used as commercially available unless stated below. All glassware was flame (or oven) dried prior to use, and reactions were performed under nitrogen atmosphere. Dichloromethane, *tert*-butanol, toluene, and DME was purified by distillation over CaH_2 at normal pressure and stored over 4Å molecular sieves. DMF and ethyl acetate were purified by vacuum distillation over CaH_2. THF was dried over metallic sodium right before the reaction was performed. Acrolein was purified by vacuum distillation over anhydrous $CaSO_4$, and stored with a small amount of hydroquinone. Diisopropylamine was vacuum distilled over NaH and stored over 4Å molecular sieves. α-Tetralone was purified by distillation under ambient pressure. *p*-Toluenesulfonic was purified by recrystallization from water. TLC samples were prepared using Merck Silica Gel 60 aluminum coated plates. Spots were visualized with a UV lamp, iodine chamber or a *p*-anisaldehyde dip. Column chromatography used Fisher 70-230 MESL (60 Å) silica gel. A Hewlett Packard 5890 series was used for GC analysis. ^{1}H, ^{13}C and ^{31}P NMR spectra were acquired on a 400MHz Bruker Avance spectrometer. All NMR samples used $CDCl_3$ as the solvent with 0.05% TMS. ^{13}P NMR spectra were referenced using an external standard of concentrated H_3PO_4 solution.

Ethyl 3-hydroxy-4-pentenoate (43). In a 500mL round bottom flask, diisopropylamine (16.1mL, 0.115mol, 1.10 equiv) and 300mL distilled THF was stirred at -78°C for 15 minutes. *n*-BuLi (46mL, 2.50M, 0.240mol, 1.2 equiv) was added dropwise via syringe and the solution was allowed to stir for 10 minutes. Ethyl acetate (10.3mL, 0.105mol, 1.0 equiv) was added and the solution was allowed to stir at -78°C for one hour. Acrolein (7.0mL, 0.104mol, 1.0 equiv) was added, and the solution was stirred at -78°C for another 4 hours. The solution was quenched by 10mL saturated NH_4Cl, and extracted 5 times with 10mL of ether. The solvent was evaporated to give a colorless liquid. (TLC

R_f=0.58 in 1:1 Hexane:EtOAc), (5.50g, 38.2% yield) ^{1}H NMR:δ 1.28 (t, J = 7.1Hz, 3H), 2.52 (dd, J=16.1, 8.2Hz, 1H), 2.59 (dd, J=16.2, 4.3Hz, 1H), 3.19 (s, 1H), 4.18 (q, J = 7.2Hz, 2H), 4.51-4.58 (m, 1H), 5.16 (dt, J=9.3, 1.2Hz, 1H), 5.32 (dt, J=17.2, 1.3Hz, 1H), 5.89 (ddd, J = 17.2, 10.5, 5.5 Hz, 1H); Lit. ^{1}H NMR: δ 1.26 (t, J = 7.1Hz, 3H), 2.50 (dd, J = 16.1, 8.7Hz, 1H), 2.57 (dd, J = 16.1, 4.6Hz, 1H), 3.02 (s, 1H), 4.16 (q, J = 7.1Hz, 2H), 4.53 (ddd, J = 8.7, 4.6, 2.8 Hz, 1H), 5.14 (ddd, J = 10.5, 1.4, 1.4Hz, 1H), 5.31 (ddd, J = 17.1, 1.4, 1.4 Hz, 1H), 5.87 (ddd, J = 17.1, 10.5, 1.4Hz, 1H).[43]

Ethyl penta-2,4-dienoate (44). The reaction followed similar procedure as previously described, using 7.7mL of diisopropylamine (54.9mmol, 1.10 equiv), 200mL THF, 22mL of *n*-BuLi (2.50M, 58.2mmol, 1.2 equiv), and 4.92mL of ethyl acetate (50mmol, 1.0equiv). Acrolein (3.4mL, 50.0mmol, 1.0 equiv) was added, and the solution was stirred at -78°C for another 4 hours. After the reaction was completed, the solution was quenched by 10mL of saturate NH_4Cl, and extracted 5 times with 10mL of ether. An additional wash of 50mL of 1M HCl was used, followed by a wash of 50mL distilled water. The solvent was evaporated to give yellowish oil as the crude product. The oil was then vacuum distilled to afford the pure yellow oil. (TLC R_f=0.73 in 1:1 Hexane:EtOAc), (2.18g, 34.6% yield) ^{1}H NMR:δ 1.30 (t, J=7.1Hz, 3H), 4.21 (q, J=7.2Hz, 2H), 5.49 (d, J=10.3Hz, 1H), 5.61 (d, J=16.6Hz, 1H), 5.91 (d, J=16.6Hz, 1H), 6.46 (dt, J=17.0, 10.3Hz, 1H), 7.26 (dd, J=15.6, 11.0Hz, 1H).

Ethyl 3-oxo-4-pentenoate (45, Method A). Alcohol **43** (0.500g , 3.47mmol, 1.0 equiv), pyridinium dichromate (2.61g, 6.94mmol, 2.0 equiv), and 3Å molecular sieves (1.22g) were added to 40mL of dry dichloromethane in a 100mL round bottom flask. The solution was stirred overnight, and the solution was filtered through Celite to remove

excess dichromate. The solution was washed with 20mL of 1M HCl follwed by 20mL of saturated NaCl. The crude product was purified by silica gel (93:7 Hexane:EtOAc) to afford colorless oil as the final product. (TLC R_f= 0.70 in 1:1 Hexane:EtOAc) (0.04g, 0.81% yield).

Ethyl 3-oxo-4-pentenoate (45, Method B). Alcohol **43** (0.50g , 3.47mmol, 1.0 equiv) and MnO_2 (3.40g, 39.1mmol, 11.3 equiv) were added to 50mL of dry dichloromethane in a 100mL round bottom flask. The solution were stirred for 4 hours, and then filtered through Celite to remove the manganese. The solvent was evaporated by blowing air over the sample to yield light yellow oil as the product. (TLC R_f= 0.70 in 1:1 Hexane:EtOAc) (0.448g, 91% crude yield).

2-Methyl-2-(3-oxopentyl)-1,3-cyclohexanedione (49a). In a 100mL three-neck round bottom flask, 5.00g (39.6mmol, 1.0 equiv.) of 2-methyl-1,3 cyclohexanedione and 0.07g (1.2mmol, 0.032 equiv.) of potassium hydroxide were dissolved in 30mL anhydrous methanol and heated at reflux for 15 minutes. Ethyl vinyl ketone (5.0mL, 50.2mmol, 1.27 equiv.) was added dropwise via addition funnel over 30 minutes, and then heated at reflux for 24 hours. Upon completion, the solution was extracted five times with 10mL ether, followed by a 10mL saturated NaCl wash. The solvent was evaporated to yield yellow oil. The crude product was purified by vacuum distillation at 129-141°C to yield the pure compound. (TLC R_f=0.40 in 1:1 Hexane:EtOAc) (5.33g, 64.1% yield). ^{1}H NMR: δ 0.94-0.98 (m, 3H); 1.18 (s, 3H); 1.83-1.93 (m, 2H); 1.99-2.01 (m, 2H); 2.25-2.26 (m, 2H); 2.31-2.35 (m, 2H); 2.59-2.60 (m, 2H); 2.67-2.70 (m, 2H).

***(S)*-3,4,8,8a-Tetrahydro-5,8a-dimethyl-1,6(2*H*,7*H*)-naphthalenedione (50a, Method B).** Triketone **49a** (3.50g, 16.6mmol, 1.0 equiv), L-phenylalanine (3.00 g,

18.2mmol, 1.10 equiv) and D-camphorsulfonic acid (2.00g, 8.61mmol, 0.52 equiv) were dissolved in 150mL dry DMF in a 300mL round bottom flask. The solution was heated to 30°C, and raised 10°C degree each day to 70°C. The solution was quenched by 20mL of saturated sodium bicarbonate and washed with 20mL saturated NaCl. A dark brown oil was obtained as crude product. (TLC R_f=0.45 in 1:1 Hexane:EtOAc) (0.76, 22.7% yield), ^{1}H NMR: δ 1.43 (s, 3H), 1.82 (d, J=1.3Hz, 3H), 2.04-2.18 (m, 4H), 2.40-2.55 (m, 4H), 2.69 (ddd, J = 15.9, 10.4, 5.9Hz, 1H), 2.88 (dtd, J=16, 5.0, 1.0Hz, 1H); Lit. ^{1}H NMR: δ 1.4 (s. 3H), 1.8 (s, 3H), 1.7-3.2 (m, 10H).[23]

***(S)*-3,4,8,8a-Tetrahydro-5,8a-dimethyl-1,6(2*H*,7*H*)-naphthalenedione (50a, Method C)**. Triketone **49a** (1.48g, 7.04mmol, 1 equiv) and L-phenylalanine (1.36g , 8.23mmol, 1.17 equiv) were added to 65mL of glacial acetic acid in a 100mL round bottom flask. The solution was heated at reflux for 24 hours. It was then extracted twice with 20mL of dichloromethane, and the organic extract was washed with 20mL of saturated sodium bicarbonate to remove all the acid. The solution was washed with 20mL saturated NaCl and the solvent was evaporated to yield the crude product as a dark brown oil. The crude product was vacuum distilled at 132-147°C to yield pure product (1.02g, 75.4% yield).

***(S)*-3',4',8',8'a-Tetrahydro-5',8'a-dimethylspiro[1,3-dioxolane-2,1'(2'*H*)-naphthalen]-6'(7'*H*)-one (51a)**. Decalin **50a** (0.50g, 2.81mmol, 1.0 equiv.) was added to 40mL of toluene in a 100ml round bottom flask fitted with a Dean-Stark trap. While stirring, 1.0mL of ethylene glycol (17.9mmol, 6.4equiv.) and a small portion of *p*-toluenesulfonic acid monohydrate were added. The mixture was heated at reflux for 4 days. The solution was then washed with 10mL saturated sodium bicarbonate, and the solvent was evaporated to yield the crude product. The crude product was purified over

column silica gel (62: 38 Hexane:EtOAc) to yield light yellow oil as final product. (TLC R_f=0.42 in 1:1 Hexane:EtOAc), (0.376g, 56.6% yield), ^{1}H NMR: δ 1.34 (s, 3H), 1.63-1.72 (m, 2H), 1.80 (d, 3H), 2.15-2.20 (m, 4H), 2.23-2.47 (m, 3H), 2.69 (ddt, J=13.3, 4.0, 1.6Hz, 1H), 3.91-4.00 (m, 4H); Lit. ^{1}H NMR: δ 1.30 (s, 3H), 1.75 (s, 3H), 1.3-1.9 (m, 10H), 3.92 (s, 4H).[23]

2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (49b). This reaction followed the same procedure as in **40a**, using 5.00g (39.6mmol, 1.0 equiv.) of 2-methyl-1,3-cyclo-hexadione and 0.07g (1.2mmol, 0.032 equiv) of KOH, and 5.0mL methyl vinyl ketone (60.1mmol, 1.52 equiv). The crude product was purified by vacuum distillation at 145-167°C to afford brown thick oil. (TLC R_f=0.38 in 1:1 Hexane:EtOAc) (5.26, 54.8% yield), ^{1}H NMR: δ 1.21 (s, 3H); 1.88-1.91 (m, 2H); 2.07 (s, 3H); 2.30-2.31 (m, 4H); 2.57-2.70 (m, 4H). ^{13}C NMR: δ 18.57, 20.22, 23.24, 26.56, 34.94 (2C), 47.95, 80.22, 209.56 (2C), 209.86.

***(S)*-3,4,8,8a-Tetrahydro-8a-methyl-1,6(2*H*,7*H*)-naphthalenedione (50b, Method B)**. This reaction followed the same procedure as in **50b** (Method B), using triketone **49b** (3.50g, 17.8mmol, 1.0 equiv), L-phenylalanine (3.00 g, 18.2mmol, 1.02 equiv) and D-camphorsulfonic acid (2.00g, 8.61mmol, 0.52 equiv). (TLC R_f=0.50 in 1:1 Hexane:EtOAc) (0.82g, 25.9% yield).

***(S)*-3,4,8,8a-Tetrahydro-8a-methyl-1,6(2*H*,7*H*)-naphthalenedione (50b, Method C)**. This reaction followed the same procedure as in **50b** (Method C), using triketone **49b** (5.00g, 25.5mmol, 1.0 equiv) and L-phenylalanine (8.41g, 50.9mmol, 2.0 equiv) added to 65mL of glacial acetic acid. The crude product of an oil was redissolved in 3mL of 1:1 Hexane:EtOAc solution and stored in freezer to afford a mixture of colorless and brown

crystals. The crude product was purified by column chromatography (45:55 Hexane:EtOAc) to give light brown oil. The oil was stored in the freezer and crystallized into small needles. (2.36g, 52.0% yield), ^{1}H NMR: δ 1.46 (s, 3H), 1.72 (qt, J=13.6, 4.3Hz, 1H), 2.10-2.20 (m, 3H), 2.43-2.54 (m, 4H), 2.70-2.77 (m, 2H), 5.86 (d, 1.8Hz, 1H); ^{13}C NMR: δ 22.84, 23.21, 29.61, 31.68, 33.54, 37.59, 50.53, 125.76, 165.77, 198.23, 210.97ppm; Lit. ^{1}H NMR: δ 1.46 (s, 3H), 1.66-1.77 (m, 1H), 2.11-2.19 (m, 3H), 2.44-2.53 (m, 4H), 2.67-2.77 (m, 2H) 5.86 (s, 1H).[44]

***(S)*-3',4',8',8'a-Tetrahydro-8'a-methylspiro[1,3-dioxolane-2,1'(2'*H*)-naphthalen]-6'(7'*H*)-one (51b)**. This reaction followed the same procedure as in **51a** using decalin **50b** (0.258g, 1.45mmol, 1.0 equiv.), 1.0mL of ethylene glycol (17.9mmol, 6.4equiv.), plus a small portion of *p*-toluenesulfonic acid monohydrate in 40mL of toluene. The apparatus was fitted with a Dean-Stark trap was heated at reflux for 1 day. The solution was then washed with 10mL saturated sodium bicarbonate, and the solvent was evaporated to yield the crude product. The crude product was purified over column silica gel (60: 40 Hexane:EtOAc) to yield light yellow oil as final product. (TLC R_f=0.29 in 1:1 Hexane:EtOAc) (0.0998g, 31.0% yield), ^{1}H NMR: δ 1.30 (s, 3H), 1.65-1.84 (m, 4H), 2.25 (dd, J=13.2, 2.5Hz), 2.37-2.48 (m, 3H), 2.54-2.62 (m, 1H), 2.64-2.69 (m, 1H), 3.87-4.01 (m, 4H), 5.57 (d, J=2.0Hz, 1H); Lit. ^{1}H NMR: δ 1.37 (s, 3H), 1.64-1.76 (m, 3H), 1.78-1.84 (m, 1H), 1.88-1.95 (m, 1H), 2.27-2.39 (m, 2H), 2.40-2.49 (m, 3H), 3.94-4.43(m, 4H), 5.83 (d, J = 1.8Hz, 1H).[45]

1,3-Bis(diethylphosphono)-2-propanone (35). In a 50mL round bottom flask, 1,3-dichloroacetone (1.88g, 14.8mmol, 1.0equiv.) and methyl hydrazinocarboxylate (1.47g, 16.3mmol, 1.1equiv.) were added to 15.6mL ethanol. After stirring for 3 hours at room temperature, the mixture turned cloudy white and it was then vacuum filtered. The

filtrate was stored in the freezer overnight and then vacuum filtered again to afford additional product. The white solid was dried in a dessicator overnight to give the final product (2.16g product, 73.3% yield).

To a 100mL 3-neck round bottom flask, 2.10g of hydrazone (10.5mmol, 1.0equiv.) 50mL distilled toluene were added. The solution was heated to reflux, followed by dropwise addition of triethyl phosphite (3.9mL, 23.2mmol, 2.2equiv.) via syringe. After heaing for 5 hours, the solvent was removed. The crude oil was transferred into a separatory funnel and 30mL of H_2O was added. The solution was extracted three times with 10mL of CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$. The solvent was removed by rotary evaporation to give light yellow oil of bisphosphonohydrazone (2.97g, 59.0% yield).

In a 50mL round bottom flask, bisphosphonohydrazone (2.60g, 6.46mmol, 1.0equiv.) and 3M HCl (7.0mL, 21mmol, 3.3equiv.) were added to a 7mL of acetone. The mixture was stirred at room temperature for 5 hours, and then 5mL of water was added to the round bottom flask. The acetone was removed by rotary evaporation and the residue was extracted three times with 10mL CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated to afford the crude product. It was purified by column chromatography (95:5 CH_2Cl_2:MeOH) to give yellow oil as the final product. (0.32g, 15.0% yield).

General procedure for monocondensation reaction of bisphosphonate

1,3-Bis(diethylphosphono)-2-propanone (0.25g, 0.757 mmol, 1.0 equiv) and 10 mL THF was added to a 25mL round bottom flask. The solution was stirred in an ice bath for 5 minutes, and sodium hydride (60% dispersion in mineral oil, 0.061g, 0.92mmol, 1.22

equiv) was added to the solution. After 30 minutes of stirring, *n*-BuLi (0.316mL, 2.5M, 0.79mmol, 1.04 equiv) was added, and the solution was stirred for another 90 minutes at 0°C. In a 100mL round bottom flask, the aldehyde (0.8mmol, 1.06 equiv) and 50mL THF were mixed in an ice bath. The 1,3-bis(diethylphosphono)-2-propanone **35** solution was slowly transferred via cannula into the aldehyde solution, and an additional 2mL of THF was used to rinse the flask. The mixture was allowed to stir overnight. Upon completion, the solution was quenched with 20mL saturated ammonium chloride and 10mL deionized water in an ice bath. The solution was extracted three times with 15mL diethyl ether. The combined organic layer was washed twice with 15mL saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The organic solvent was rotary evaporated to yield the crude oil, which was purified via column chromatography (98:2 dichrolomethane : 2-propanol) to yield the final product.

1,7-Di(3-methoxyphenyl)hepta-1,6-diene-3,5-dione (64). The reaction followed the general monocondensation reaction using *m*-anisaldehyde (97.3µl, 0.80mmol) as the reagent to afford a yellowish oil. However, the ^{1}H NMR spectrum suggested the final product was the dicondensate. (TLC R_f=0.33 in 98:2 CH_2Cl_2:2-propanol)(0.1133g, 84.2% yield) ^{1}H NMR: δ 3.85(s, 3H), 6.96 (dd, J = 10.4, 4.7Hz, 1H), 7.07 (d, J = 15.9Hz, 1H), 7.13 (t, J = 1.9Hz, 1H), 7.21 (d, J = 7.7Hz, 1H), 7.33 (d, J = 7.9Hz, 1H), 7.70 (d, J = 15.96Hz, 1H).

Diethyl 4-(4-bromophenyl)-2-oxobut-3-enylphosphonate (65). The reaction followed the general monocondensation reaction using *p*-bromobenzaldehyde (0.148g, 0.80mmol) as the reagent. After column chromatography, the final product was obtained. The final product crystallized after the solvent was removed, giving rectangular white crystals. (0.084g, 30.7% yield); ^{1}H NMR: δ 1.33 (t, J = 7.1Hz, 6H), 3.31 (d, J_{HP} = 22.7Hz, 2H),

4.11-4.19 (m, 4H), 6.88 (d, J = 16.0Hz, 1H), 7.43 (d, J = 8.5Hz, 2H), 7.53 (d, J = 8.5Hz, 2H), 7.57 (d, J = 16.1Hz, 1H). ^{13}C NMR: δ 16.3 (d, J_{CP} = 6.3Hz, 2C), 41.3 (d, J_{CP} = 128Hz), 62.6 (d, J_{CP} = 6.4Hz, 2C), 125.2, 126.1 (d, J_{CP} = 1.0Hz), 132.2 (2C), 133.1, 143.1 (2C), 190.8 (d, J_{CP} = 6.1Hz); ^{31}P NMR: δ 19.20.

Diethyl 4-(3,4,5-trimethoxyphenyl)-2-oxo-but-3-enylphosphonate (66). The reaction followed the general monocondensation reaction using 3,4,5-trimethoxybenzaldehyde (0.133g, 0.68mmol) as the reagent. After column chromatography, the final product of yellow oil was obtained. (0.1192g, 47.1% yield); ^{1}H NMR: δ 1.22 (t, J = 7.1Hz, 6H), 3.21 (d, J_{HP} = 22.6Hz, 2H), 3.76 (s, 3H), 3.77 (s, 6H), 4.04–4.20 (m, 4H), 6.69 (d, J = 15.9Hz, 1H), 6.69 (s, 2H), 7.45 (d, J = 15.9Hz, 1H); ^{13}C NMR: δ 16.2 (d, J_{CP} = 6.5Hz, 2C), 40.7 (d, J_{CP} = 128Hz), 55.8, 60.8, 62.5 (d, J_{CP} = 6.6Hz, 2C), 105.7, 125.0, 129.5 (2C), 140.5, 144.8 (2C), 153.3, 190.8 (d, J_{CP} = 5.8Hz); ^{31}P NMR: δ 19.47.

Diethyl 4-(2,5-dimethoxyphenyl)-2-oxobut-3-enylphosphonate (67). The reaction followed the general monocondensation reaction using 2,5-dimethoxybenzaldehyde (0.157g, 0.80mmol) as the reagent. After column chromatography, the light yellow oil was obtained as the final product. (0.1037g, 37.9% yield); ^{1}H NMR: δ 1.33 (t, J = 7.1Hz, 6H), 3.35 (d, J_{HP} = 22.6Hz, 2H), 3.79 (s, 3H), 3.85 (s, 3H), 4.11–4.22 (m, 4H), 6.86 (d, J = 9.1Hz, 1H), 6.89 (d, J = 16.3Hz, 1H), 6.94 (dd, J = 9.0, 3.0Hz, 1H), 7.08 (d, J = 3.0Hz, 1H), 7.94 (d, J = 16.3Hz, 1H); ^{13}C NMR: δ 16.0 (d, J_{CP} = 6.6Hz, 2C), 40.1 (d, J_{CP} = 127.7Hz), 55.5, 55.8, 62.3 (d, J_{CP}=6.8Hz, 2C), 112.2, 112.7, 117.9, 123.3, 126.2, 139.6, 153.1, 191.3 (d, J_{CP} = 6.4Hz); ^{31}P NMR: δ 19.70.

Diethyl 4-(2,3-dimethoxyphenyl)-2-oxobut-3-enylphosphonate. The reaction followed the general monocondensation reaction using 2,3-dimethoxybenzaldehyde (0.157g,

0.80mmol) as the reagent. However, the reaction failed to yield the product.

Diethyl 6-(2-methoxyphenyl)-2-oxohexa-3,5-dienylphosphonate (68). The reaction followed the general monocondensation reaction using 2-methoxycinnamaldehyde (0.135g, 0.80mmol) as the reagent. After column chromatography, the final product was obtained. (0.1990g product, 73.5% yield) ^{1}H NMR: δ 1.33 (t, J = 7.6Hz, 6H), 3.26 (d, J_{HP} = 22.6Hz, 2H), 4.10–4.19(m, 4H), 6.38 (d, J = 15.3Hz, 1H), 6.89 (d, J = 8.3Hz, 1H) , 6.94 (t, J = 7.7Hz, 1H), 6.96 (dd, J = 15.6, 10.9Hz, 1H), 7.29 (td, J = 7.7, 1.6Hz, 1H), 7.35 (d, J = 15.6Hz, 1H), 7.44 (dd, J = 15.3, 11.1Hz, 1H), 7.49 (dd, J = 7.7, 1.3Hz, 1H); ^{13}C NMR: δ 16.0 (d, J_{CP} = 6.0Hz, 2C), 40.2(d, J_{CP} = 127.1Hz), 55.2, 62.2 (d, J_{CP} = 6.6Hz), 110.8, 120.4, 124.4, 126.6, 127.3, 128.2, 130.4, 137.6, 145.7, 157.3, 190.7 (d, J_{CP} = 6.2Hz); ^{31}P NMR δ 19.17.

Diethyl 6-(2-nitrophenyl)-2-oxohexa-3,5-dienylphosphonate (69). The reaction followed the general monocondensation reaction using *o*-nitrocinnamaldehyde (0.141g, 0.80mmol) as the reagent. After column chromatography, a very dark colored product was obtained. (0.1783g, 66.7% yield) ^{1}H NMR: 1.34(t, J = 7.1Hz, 6H), 3.29(d, J_{HP} = 22.6Hz, 2H), δ 4.11–4.21(m, 4H), 6.49(d, J = 15.4Hz, 1H), 6.87(dd, J = 15.4, 11.0Hz, 1H) , 7.43(dd, J = 15.7, 11.3Hz, 1H), 7.48(d, J = 15.9Hz, 1H), 7.49(d, J = 8.2Hz, 1H), 7.64(t, J = 7.4Hz, 1H), 7.70(d, J = 6.9Hz, 1H), 7.99(dd, J = 8.1, 1.0Hz, 1H); ^{13}C NMR: δ 16.2 (d, J_{CP} = 7.9Hz, 2C), 40.1 (d, J_{CP} = 127.8Hz), 62.5 (d, J_{CP}=6.9Hz, 2C), 124.8, 128.2, 129.3, 130.9, 131.2, 133.2, 136.3, 143.4, 147.8, 190 (d, J_{CP} = 6.2Hz); ^{31}P NMR δ 19.73.

2,2-Dimethylcyclohexanone (55, Method A). In a 50mL round bottom flask containing KH (1.52g, 37.9mmol, 1.05 equiv), a small amount of THF (10mL), 2-methylcyclo-

hexanone (4.038g, 36mmol) and Et_3B (4.5mL, 45.0mmol, 1.25equiv) was added. The solution was stirred under nitrogen atmosphere at room temperature. After one day, MeI (6.8mL, 108mmol, 3.0equiv) was added dropwise into the round bottom flask. The solution was stirred for another 24 hours and quenched by saturated NH_4Cl (20mL). The aqueous layer was extracted three times with 10mL of ether. The combined organic mixture was dried over $MgSO_4$. The solvent was evaporated to give a yellow oil as the crude product. The product was purified via vacuum distillation (60°C, 1 torr) to yield the final product. ^1H NMR spectrum suggested not only the desired product, but also methylation at C-6 as well. (TLC R_f = 0.80 in 30:70 Hexanes:EtOAc), (1.73g, 38.1% yield), ^1H NMR: δ 0.99(d, J = 7.1Hz, 3H), 1.03(d, J = 6.2Hz, 6H), 1.04(s, 2.7H), 1.11(s, 3H), 1.18(s, 2.7H).

2,2-Dimethylcyclohexanone (55, Method B). In a 50mL round bottom flask containing KOH (12.1g, 216mmol, 6.0 equiv), a small amount of THF (10mL) and 2-methylcyclohexanone (4.038g, 36mmol, 1.0 equiv) was added. The solution was stirred under nitrogen atmosphere at room temperature. After one day, MeI (2.67mL, 43.2mmol, 1.2equiv) was added dropwise into the round bottom flask. The solution was stirred for another 24 hours and quenched by saturated NH_4Cl (20mL). The aqueous layer was extracted three times with ether (10mL). The combined organic mixture was dried over $MgSO_4$, and the solvent was evaporated to give the crude product. (1.68g, 37.0% yield) GC and ^1H NMR of the crude product suggested 1.25 : 1 mixture of 2,2-dimethyl and 2,6-dimethyl products (GC: Initial temp: 100°C, rate: 1°C/min, ret. time: 4.3mins, 4.6min. ^1H NMR: δ 1.03(d, J = 6.6Hz, 4.5H), 1.11(s 3H).

2-Hydroxymethylene-6-methylcyclohexanone (71, Method A). In a 100mL round

bottom flask containing anhydrous methanol (3.65mL, 90mmol, 2.0equiv) and distilled toluene (35mL) in ice bath, sodium (2.189g, 94.73mmol, 2.1equiv) was added slowly. After stirring for 10 minutes, ethyl formate (7.29mL, 90.22mmol, 2.0equiv) was added into the mixture, followed by addition of 2-methylcyclohexanone (5.5mL, 45.11mmol, 1.0 equiv). The solution was stirred for one day, and then quenched with 20mL of isopropanol followed by 20mL ice water. The aqueous layer was extracted three times with ether (10mL). The combined organic layers were washed with 25mL of saturated NaCl, and dried over $MgSO_4$. The solvent was removed by rotary evaporating to give light yellow oil as the crude product. (0.29g, 4.6% yield).

2-Hydroxymethylene-6-methylcyclohexanone (71, Method B). In a 100mL round bottom flask containing anhydrous methanol (3.65mL, 90mmol, 2.0equiv) and distilled toluene (35mL), sodium hydride (60% dispersion in mineral oil, 3.80g, 94.73mmol, 2.1equiv) was added slowly in an ice bath. After stirring for 10 minutes, ethyl formate (7.29mL, 90.22mmol, 2.0equiv) was added into the mixture, followed by addition of 2-methylcyclohexanone (5.5mL, 45.11mmol, 1.0 equiv). The solution was stirred for one day, and then quenched with isopropanol (20mL) followed by ice water (20mL). The aqueous layer was extracted three times with ether (10mL). The combined organic layers were washed with 25mL saturated NaCl, and dried over $MgSO_4$. The solvent was removed by rotary evaporation to yield colorless oil as the crude product. ^1H NMR indicated the presence of impurities, but the sample was pure enough for next reaction without further purification. (7.65g, 121% yield), ^1H NMR: δ 1.02 (d, J = 6.2Hz, 3H), 1.19-1.44 (m, 2H), 1.55-2.06 (m, 4H), 2.22-2.51 (m, 1H), 8.61(d, J = 3.4Hz, 1H), 14.58(d, J = 3.4Hz, 1H); ^{13}C NMR: δ 14.72, 17.47, 20.97, 23.76, 25.17, 27.94, 30.01, 35.84, 45.36, 108.29, 128.20, 187.02.

2-Isopropoxymethylene-6-methylcyclohexanone (72). In a 100mL round bottom flask containing 30mL acetone , hydroxymethylene **71** (1.15g, 8.21mmol, 1 equiv) and K_2CO_3 (1.38g, 10.0mmol, 1.25equiv) was added with stirring at room temperature. After 10 minutes, 2-bromopropane (0.96mL, 10.0mmol, 1.25equiv) was added slowly into the solution. The reaction mixture was stirred for one day, and then the solvent was evaporated. The organic material was dissolved in 30mL ether and washed with 0.1M NaOH solution (15mL) twice, followed by a wash of saturated NaCl (20mL). The organic layer was dried over $MgSO_4$, and the solvent was removed to give yellowish oil as the product. (0.80g, 53.6% yield), ^{1}H NMR: δ 1.14 (d, J = 6.4Hz, 3H), 1.29 (dd, J = 6.1, 2.3Hz, 6H), 1.76-2.13 (m, 4H), 2.20-2.44 (m, 2H), 2.51-2.59 (m, H) 4.19 (sept, J = 6.2Hz, 1H), 7.30 (t, J = 1.9Hz, 1H).

6-Isopropoxymethylene-2,2-dimethylcyclohexanone (73). To a mixture of 30mL acetone and K_2CO_3 (0.79g, 5.7mmol, 1.3equiv), isopropyl enol **72** (0.80g, 4.40mmol, 1.0equiv) was added. After one hour of stirring at room temperature, methyl iodide (0.55mL, 8.8mmol, 2.0equiv) was added dropwise into the solution, and the reaction mixture was stirred at room temperature for one day. Water (50mL) was added, and the solution was extracted three times with ether (15mL). The combined organic mixture was washed by saturated NaCl (10mL), followed by drying over $MgSO_4$. The solvent was removed by rotary evaporation to give a brown oil as the product (0.79g, 91.5% yield). ^{1}H NMR spectroscopy reveal an absence or vinyl proton peak at δ 7.30, suggesting the protecting group fell off at this stage.

2,2-Dimethylcyclohexanone (55, Method C). In a 50mL round bottom flask, methylated product **73** (0.79g, 4.03mmol, 1.0equiv.) was dissolved in 10mL of 95% EtOH in ice bath.

The solution was treated with 1mL of 1.0M HCl (1.0mmol, 0.25equiv.) and stirred for an hour. Water (50mL) was added, and the solution was extracted three times with ether (15mL). The combined organic solution was dried over $MgSO_4$. The solvent was removed by rotary evaporation to give 0.23g brown oil as the final product. However, both TLC and ^1H NMR spectroscopy revealed presence of multiple products that were difficult to separate.

2,2-Dimethylcyclohexanone (55, Method D). In a 100mL three-neck round bottom flask, 2-methylcyclohexanone (7.58mL, 62.4mmol, 1.0 equiv) was dissolved in anhydrous ether (40mL). While stirring, sodium amide (2.56g, 65.6mmol, 1.05 equiv) was added into the mixture. The solution was then refluxed for an hour. After cooling down, MeI (4.1mL, 65.53mmol, 1.05 equiv) was added dropwise into the solution. The solution was heated at reflux for three days, and then washed twice with cold water (50mL), 1M tartaric acid (16mL), 1M thiosulfate solution (16 mL), and saturated sodium bicarbonate solution (16mL). The organic layer was dried over $MgSO_4$, and the solvent was removed to yield colorless liquid as the final product (5.73g, 73% yield). ^1H NMR: δ 1.11 (s, 6H), 1.64-1.69 (m, 2H), 1.70-1.78 (m, 2H), 1.79-1.87 (m, 2H), δ 2.39 (t, J=7.8Hz, 2H); Lit. ^1H NMR: δ 0.85 (s, 3H), 0.97 (s, 3H), 1.2-1.5 (m, 7H), 1.6-1.8 (m, 2H), 3.2-3.35 (m, 1H).[46]

[Hydroxy(tosyloxy)iodo]benzene (Koser's reagent). *p*-Toluenesulfonic acid monohydrate (1.73g, 9.08 mmol, 1.3 equiv) was dissolved in acetonitrile (10mL) at room temperature, and iodobenzene diacetate (2.25g, 6.99mmol, 1.0equiv) was added. The mixture was stirred for one hour and the suspension was vacuum filtered. The filtered product was washed with acetone (10mL) followed by cold ether (10mL) to remove the acidic components. The trace amount of solvent was removed by vacuum pump to give a

white powder (2.44g, 78.9% yield). m.p.: 135~138°C (lit. m.p.: 135~138°C).[37]

General Procedure for α-Tosylation. In a 25mL three-neck round bottom flask, the carbonyl compound (1.0equiv) and [hydroxy(tosyloxy)iodo]benzene (1.1 equiv) were added to dry acetonitrile solution (10mL). Depending on the nature of the starting carbonyl compound, the reaction mixture was allowed to stir under various conditions. Upon completion, the solvent was then evaporated and the organic material was dissolved in 20mL CH_2Cl_2. The solution was washed twice with water (30mL) and dried over $MgSO_4$. The solvent was removed to obtain the crude product.

1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl 4-methylbenzenesulfonate (75). α-Tetralone (0.50mL, 3.73mmol, 1.0equiv) was treated with [hydroxy(tosyloxy)iodo]benzene (1.60g, 4.08mmol, 1.1 equiv) in acetonitrile (10mL), and heated at reflux for one day. After work up, the product was purified via column chromatography (72:28 Hexanes:EtOAc) to give 0.423g brown oil as the final product (TLC $R_f = 0.29$ in 75:25 Hexane:EtOAc). ^1H NMR spectroscopy showed tosylate peaks at δ 2.35(s, 3H), 7.26(d, J = 7.7Hz, 2H), 7.86(d, J = 8.6Hz, 2H) and a-carbonyl peak at δ 5.14(dd, J = 12.3, 5.0Hz, 1H), but with a 3:1 ratio of starting material to product from integration.

2-Oxocyclohexyl 4-methylbenzenesulfonate (76). Cyclohexanone (0.15mL, 1.45mmol, 1.0 equiv) was treated with [hydroxy(tosyloxy)iodo]benzene (0.62g, 1.58mmol, 1.1equiv) in acetonitrile (10mL), and stirred at room temperature for three days. TLC indicated the reaction was not completed, so the solution was then refluxed for 10 minutes. After work up, the crude oil product was washed twice with hexane (2mL), and stored in the freezer

for one day to crystallize into pale yellow solid. (TLC R_f = 0.38 in 7:3 Hexane:EtOAc), (0.18g, 47% yield); ^{1}H NMR: δ 1.56-1.78 (m, 2H), 1.85 (dd, J = 11.6, 3.1Hz, 1H), 1.88-2.02 (m, 2H), 2.22–2.37 (m, 2H), 2.42 (s, 3H), 2.50 (dtd, J = 13.9, 4.2, 1.9Hz, 1H), 4.90 (ddd, J = 11.0, 6.0, 0.8Hz, 1H), 7.33 (d, J = 8.0Hz, 2H), 7.82 (dd, J = 8.4, 1.8Hz, 2H); Lit. ^{1}H NMR: δ 1.30-2.7 (m, 11H), 4.8 (s, 1H), 7.10-8.02 (dd, 4H).[39]

3-Methyl-2-oxocyclohexyl 4-methylbenzenesulfonate (77). 2-Methylcyclohexanone (0.16mL, 1.34mmol, 1.0 equiv) was treated with [hydroxy(tosyloxy)iodo]benzene (0.577g, 1.47mmol, 1.1equiv) in acetonitrile (10mL). The reaction mixture stirred at room temperature for 2.5 hr. After work up, the crude oil product was purified by column chromatography (Hexane:EtOAc 72:28) to give 0.059g (15.6%) racemic (1:1.03) *trans*- and *cis*- tosylated products.

trans-: (TLC R_f = 0.51 in 7:3 Hexane:EtOAc), (0.019g pure product, 5.0%); ^{1}H NMR: δ 0.93 (d, J=6.68 Hz, 3H), 1.30-1.41 (m, 1H), 1.65 (dt, J=13.6, 4.2 Hz, 1H), 1.76-1.89 (m, 1H), 1.92-2.08 (m, 2H), 2.20-2.27 (m, 1H), 2.45 (s, 3H), 2.83-2.94 (m, 1H), 4.59 (dd, J=4.6, 3.2Hz, 1H), 7.35 (d, J=8.2Hz, 2H), 7.78 (d, J=8.1Hz, 2H); ^{13}C NMR: 14.0, 19.4, 21.7, 29.7, 34.3, 36.5, 42.0, 82.1, 128.1, 129.9, 132.8, 145.2, 207.8.

(*cis*-: 0.020g pure product, 5.3%, TLC R_f = 0.40 in 7:3 Hexane:EtOAc, ^{1}H NMR: δ 1.03 (d, J=6.4 Hz, 3H), δ 1.23-1.38 (m, 1H), δ 1.74-1.85 (m, 2H), δ 1.88-1.95 (m, 1H), δ 2.01-2.11(m, 2H), δ 2.36-2.50 (m, 1H), δ 2.44 (s, 3H), δ 5.00 (dd, J=12.0, 6.4Hz, 1H), δ 7.34 (d, J=8.2Hz, 2H), δ 7.86 (d, J=8.2Hz, 2H); ^{13}C NMR: 13.8, 21.6, 23.0, 35.0, 35.5, 81.8, 127.8, 129.7, 133.9, 144.7, 203.8; Lit. ^{1}H NMR (racemic): δ 0.98 (d, 3H), 1.30-2.72 (m, 9H), 4.84-5.32 (m, 1H), 7.18-8.10 (dd, 4H).[39]

3,3-Dimethyl-2-oxocyclohexyl 4-methylbenzenesulfonate (56). 2,2-Dimethylcyclo-hexanone (150 mg, 1.189mmol, 1.0 equiv) was treated with [hydroxy(tosyloxy)iodo]-

benzene (0.49g, 1.25mmol, 1.1 equiv) in acetonitrile (10mL). The reaction mixture was heated at reflux for 1 hr. After work up, the crude oil product was washed twice with hexanes (2mL) and stored in the freezer for one day to crystallize into pale yellow solid. (TLC R_f = 0.41 in 7:3 Hexane:EtOAc), (0.122g, 35% yield); ^{1}H NMR: δ 1.04 (s, 3H), 1.14 (s, 3H), 1.51 (td, J=13.7, 3.8Hz, 1H), 1.68-1.82 (m, 3H), 1.86-1.93 (m, 1H), 2.35 (tt, J=8.8, 3.0Hz, 1H), 2.43 (s, 3H), 5.24 (dd, J=11.9, 6.5Hz, 1H), 7.33 (d, J=7.8Hz, 2H), 7.83 (dd, J=7.8, 1.7 Hz, 2H); ^{13}C NMR: δ 19.35, 21.39, 24.00, 24.80, 34.63, 40.07, 46.00, 79.27, 127.58, 129.45, 133.59, 144.57, 206.10.

1,3-Dimethyl-2-oxocyclohexyl 4-methylbenzenesulfonate (78). 2,6-Dimethylcyclohexanone (150mg, 1.189mmol, 1.0 equiv) was treated with [hydroxy(tosyloxy)iodo]-benzene (0.49g, 1.25mmol, 1.05 equiv) in acetonitrile (10mL). The reaction mixture was stirred at room temperature for one day. GC spectrum showed only the presence of the starting material, and after work up only the starting material was recovered (0.090g, 60% recovery).

3,3-Dimethyl-2-oxocyclohexyl methanesulfonate (79). 2,2-Dimethylcyclohexanone (0.50g, 3.97mmol, 1.0 equiv) was treated with [hydroxy(mesyloxy)iodo]benzene (1.71g, 4.37mmol, 1.1 equiv) in acetonitrile (10mL). The reaction was stirred at room temperature for two days. The solvent was evaporated and the crude product was dissolved in dichloromethane (20mL), washed three times with water (10mL), and saturated NaCl (20mL). The organic solvent was removed to afford the crude product as a yellow oil. Column chromatography (Hexane:EtOAc 7:3) was used to give the pure product. (TLC R_f = 0.55 in 6:4 Hexane:EtOAc), (0.435g, 49% yield,); ^{1}H NMR: δ 1.12 (s, 3H), 1.24 (s, 3H), 1.60 (td, J=13.2, 3.7Hz, 1H), 1.74–1.91 (m, 3H), 1.92–1.98 (m, 1H), 2.38–2.50 (m, 1H), 3.21 (s, 3H), 5.37 (dd, J =12.4, 6.6Hz, 1H).

Cyclohexyl 4-methylbenzenesulfonate (80) In a 50mL round bottom flask, cyclohexanol (3.00g, 29.9mmol, 1.0 equiv) was dissolved in pyridine (12mL, 149mmol, 5.0equiv.) in an ice bath. *p*-Toluenesulfonic chloride monohydrate (6.28g, 32.9mmol, 1.1 equiv) was added slowly to the reaction mixture. The solution was at 0°C for 4 hours, and water (50mL) was added. The aqueous layer was extracted three times with ether (10mL), and the combined organic layers were washed with water (10mL) and saturated NaCl solution (10mL). The solvent was removed to give light yellow oil as the crude product. The crude product was then put in a dry ice/2-propanol bath, and upon standing at room temperature final product crystallizing into colorless needles. (5.67g, 75% yield, MP = 38~41°C, Lit. m.p. = 39~42°C).[40] ^{1}H NMR: δ 1.22–1.34 (m, 3H), 1.42–1.58 (m, 3H), 1.66–1.83 (m, 4H), 2.44 (s, 3H), 4.50 (tt, J=8.9, 3.9Hz, 1H), 7.33 (d, J=8.2Hz, 2H), 7.80 (d, J=8.2Hz, 2H). Lit. ^{1}H NMR: δ 1.30-1.78 (m, 10H), 2.44 (s, 3H), 4.49 (m, 1H), 7.32 (d, J = 8.8Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H).[47]

General Procedure for Substitution Reactions. In a 50mL round bottom flask, nucleophiles (1.1 equiv) and a base (1.1 equiv) was added to the solvent. The mixture was refluxed for 30 minutes and allowed to cool to room temperature, followed by dropwise addition of the substrate. The mixture was continue to reflux for certain length of time, and washed with 0.1M HCl solution (20mL). The aqueous layer was extracted three times with ether (10mL), and the combined organic layers were washed with saturated NaCl (10mL). The solvent was evaporated and the crude material was purified by column chromatography (Hexane:EtOAc combination) to afford the product.

Variation of Substitution Reaction:

I. Substrates:

The original substrate for the phophonate reaction was tosylcyclohexane. Other substrates tested included: iodopentane, benzyl bromide, 2-chlorocyclohexanone, 6,6-dimethyl-2-tosylcyclohexanone, 2-tosylcyclohexanone, and 6,6-dimethyl-2-mesylcyclohexanone.

II. Nucleophiles:

The nucleophiles for this reaction were trimethyl phosphonoacetate, triethyl phosphonoacetate, ethyl acetate and 1-aminopentane.

III. Bases:

The base used were: NaH, metallic sodium, KH, LiCl/DBU, KO^{t}Bu, NaHMDS and MeLi.

IV. Solvents:

Solvents used in this reaction were MeOH, THF, DMF, and DME.

Cyclohexyl 2-(diethoxyphosphoryl)acetate (81). Triethyl phosphonoacetate (0.53g, 2.36mmol, 1.2equiv) was treated with NaH (60% dispersion in mineral oil, 0.08g, 2.36mmol, 1.2equiv) in 10mL DMF. The mixture was refluxed for one hour. After cooling down, tosyl cyclohexane **80** (0.50g, 1.97mmol, 1.0equiv) that 3mL DMF was cannulaed into the solution. It was heated at reflux for two days, and afforded a yellow oil as the product. (TLC R_f= 0.53 in 1:1 Hexanes:EtOAc), (0.20g, 36.5% yield); ^{1}H NMR: δ 1.22-1.29 (m,1H), 1.35 (t, J = 7.0Hz, 3H), 1.40-1.58 (m, 4H), 1.69-1.91 (m, 5H), 2.96 (d, J_{HP} = 21.4Hz, 2H), 4.16 (q, J = 7.1Hz, 1H), 4.19(q, J = 7.1Hz, 1H), 4.81 (tt, J = 8.9, 4.0Hz, 1H). ^{13}C NMR: δ 16.29 (d, J_{CP}= 6.2Hz, 2C), 23.55 (2C), 25.23, 31.36 (2C), 34.63 (d, J_{CP}= 133Hz), 62.55 (J_{CP}= 6.1Hz, 2C), 73.99, 165.20.

Ethyl 2-(diethoxyphosphoryl)-3-phenylpropanoate (82). Triethyl phosphonoacetate

(1.13g, 5.05mmol, 1.2equiv) was treated with NaH (60% dispersion in mineral oil, 0.20g, 5.05mmol, 1.2equiv) and one drop of 15-crown-5 in 10mL DMF. The mixture was refluxed for one hour. After cooling down, benzyl bromide (0.50mL, 4.21mmol, 1.0equiv) was added dropwise by a syringe into the solution. It was stirred at room temperature and after work up gave a yellow oil. The product was purified by column chromatography (80:20 Hexanes:EtOAc) to afford pale yellow oil. (TLC R_f=0.35 in 8:2 Hexanes:EtOAc), (0.20g, 15.1% yield); ^{1}H NMR: δ 1.14 (t, J=7.0Hz, 3H), 1.35 (td, J=7.1, 1.8Hz, 6H), 3.17-3.32 (m, 1H), 4.06-4.13 (m, 2H), 4.13-4.23 (m, 4H), 7.20 (d, J=12.7, 2H), 7.27 (t, J=7.0Hz, 2H), 7.33-7.42 (m, 1H); ^{13}C NMR: 13.74, 16.16 (d, J_{CP} = 2.9Hz, 2C), 32.52 (d, J_{CP} = 4.4Hz), 47.44 (d, J_{CP} = 127Hz), 61.10, 62.54 (d, J=6.7Hz), 62.70 (d, J=6.4Hz, 2C), 126.46 (2C), 128.26 (2C), 128.35, 138.24 (d, J_{CP} = 16.2Hz), 168.25 (d, J_{CP} = 4.5Hz).

Diethyl 3-(2-chlorocyclohexylidene)-2-oxopropylphosphonate (83). Triethyl phosphonoacetate (0.53g, 2.36mmol, 1.2equiv) was treated with NaH (60% dispersion in mineral oil, 0.08g, 2.36mmol, 1.2equiv) in 10mL THF, and the mixture was refluxed for one hour. After cooling down, 2-chlorocyclohexanone (0.23mL, 1.97mmol, 1.0equiv) was added dropwise. It was stirred at room temperature and after work up gave a brown oil. The product was purified by column chromatography (3:97 Hexanes:EtOAc) to afford yellow oil as the final product. (TLC R_f= 0.43 in 3:97 Hexanes:EtOAc), (0.19g, 47.5% yield); ^{1}H NMR: δ 1.28 (t, J = 7.1Hz, 9H), 1.56-1.66 (m, 2H), 1.80-2.17(m, 5H), 2.29-2.43 (m, 1H), 2.70-2.98 (m, 2H), 3.11(td, J = 14.1, 5.0Hz, 1H), 4.16 (qd, J = 7.1, 1.6Hz, 4H), 5.90 (s, 1H).

Ethyl 2-(cyclohex-2-enylidene)acetate (84) Triethyl phosphonoacetate (0.244g, 1.09mmol, 1.2equiv) was treated with of NaH (60% dispersion in mineral oil, 0.05g, 1.09mmol, 1.2equiv) in 10mL DME. The mixture was refluxed for one hour. After

cooling down, 3,3-dimethyl-2-oxocyclohexyl methanesulfonate (**79**) (0.14g, 0.908mmol, 1.0equiv) in 3mL DME was cannulaed into the solution, and it was heated at reflux for two days to afford an oil. The product was purified by column chromatography (80:20 Hexanes:EtOAc) to afford yellow oil as the final product. (TLC R_f = 0.72 in 60:40 Hexanes:EtOAc), (0.14g product, 41.0%); ^{1}H NMR: 0.88 (t, J=6.9Hz, 3H), 1.48-1.88 (m, 6H), 2.04 (s, 3H), 2.35-2.55 (m, 1H), 3.58 (dt, J=14.0, 4.1Hz, 1H), 4.12 (q, J=7.3Hz, 2H), 4.16 (q, J=7.2Hz, 1H), 5.91 (s, 1H); ^{13}C NMR: δ 14.11, 22.61, 22.91, 31.31, 38.41, 59.65, 80.50, 112.31, 161.51, 171.3.

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Appendix - NMR Spectra of Compounds

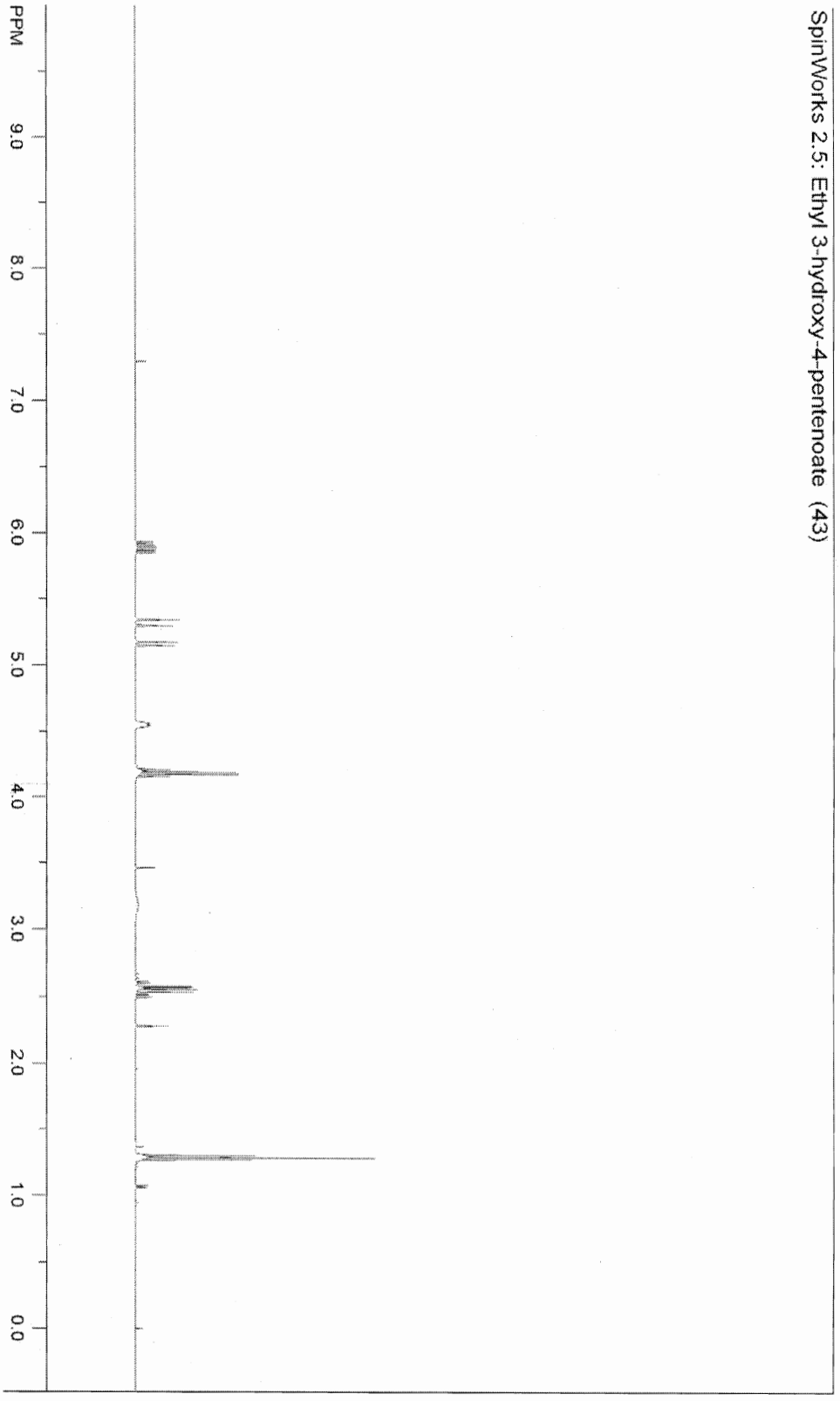

Figure 20. ^{1}H NMR Spectrum of Ethyl 3-hydroxy-4-pentenoate **(43)**.

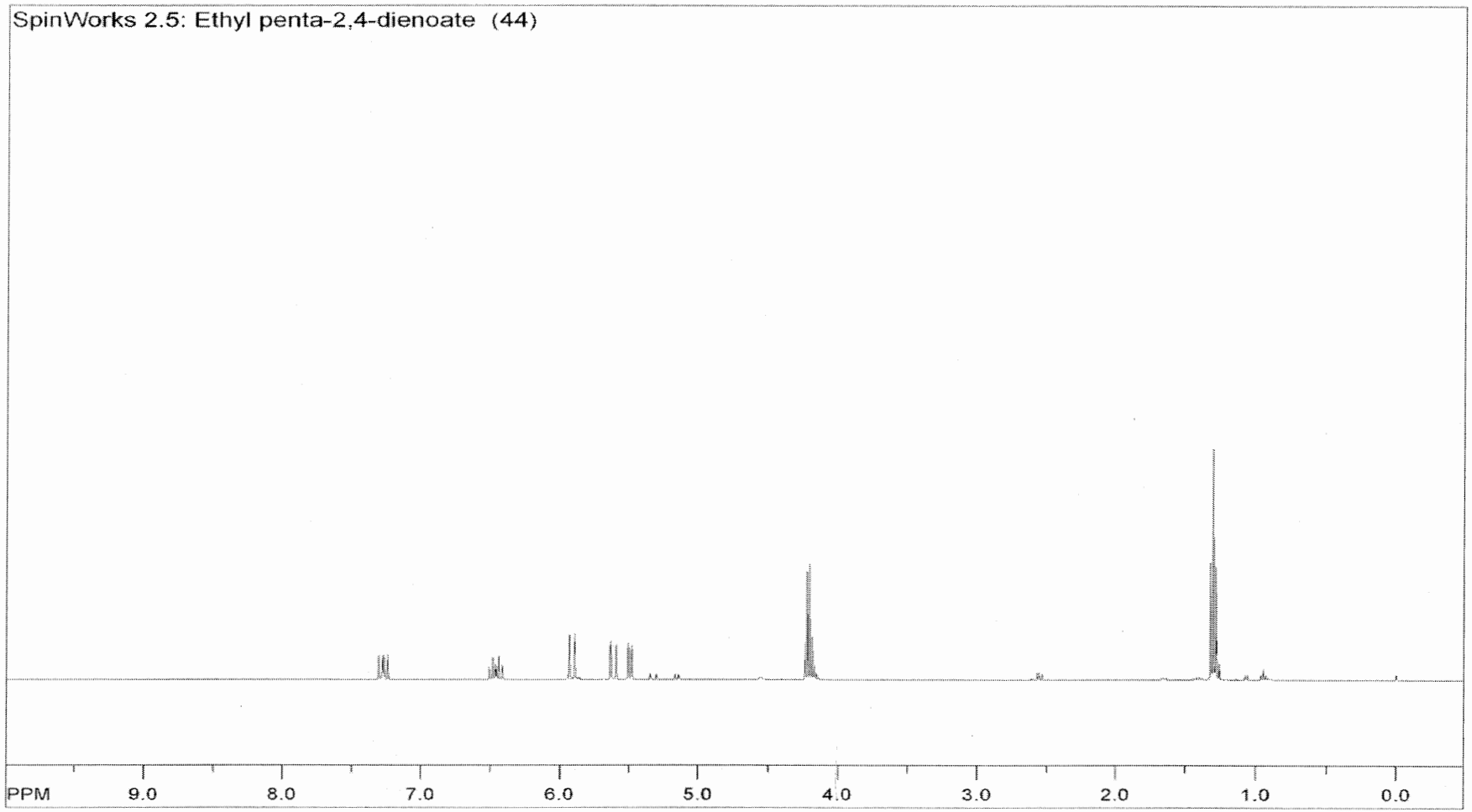

Figure 21. ^{1}H NMR Spectrum of Ethyl penta-2,4-dienoate **(44)**.

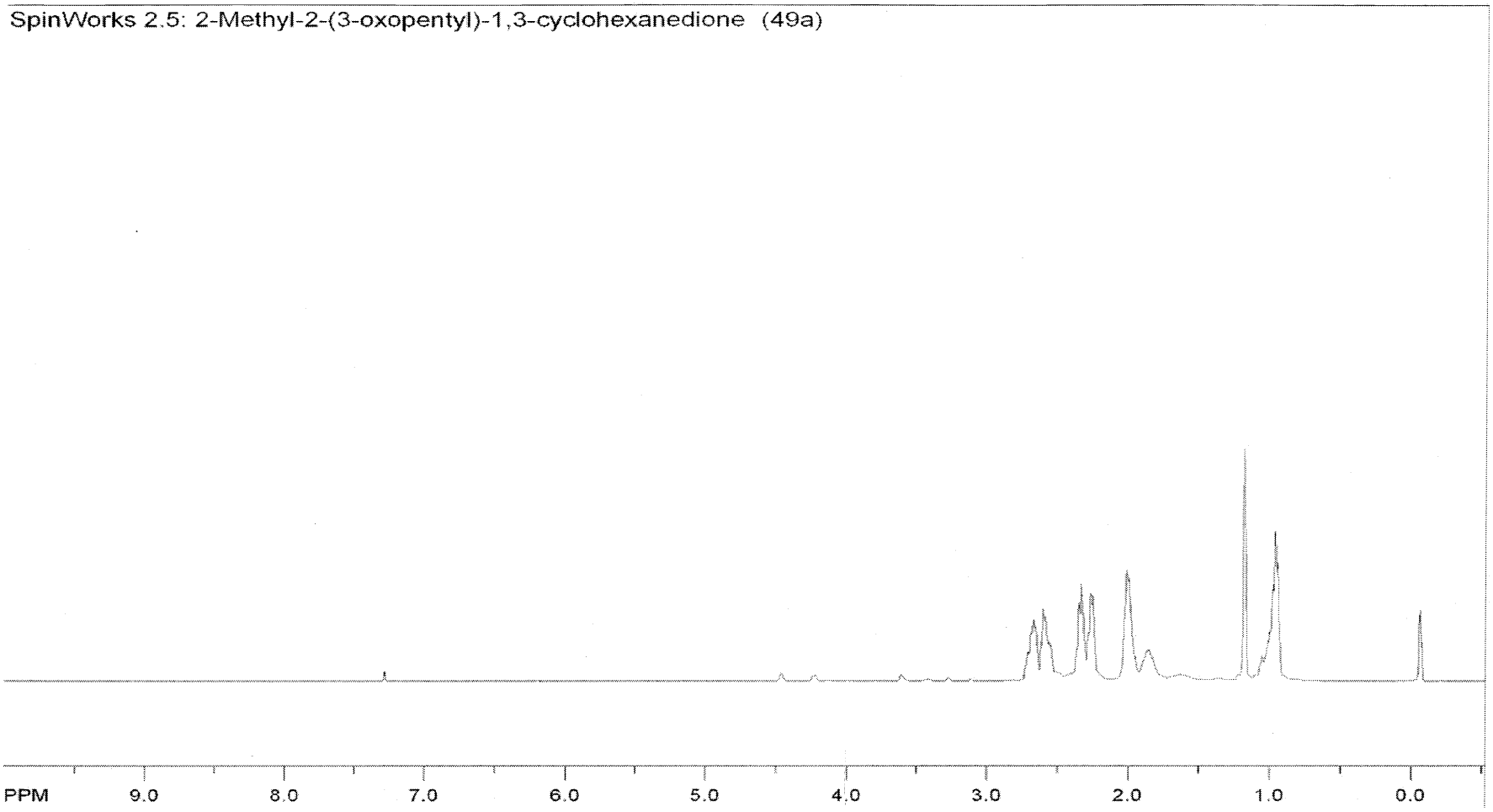

Figure 22. ^{1}H NMR Spectrum of 2-Methyl-2-(3-oxopentyl)-1,3-cyclohexanedione **(49a)**.

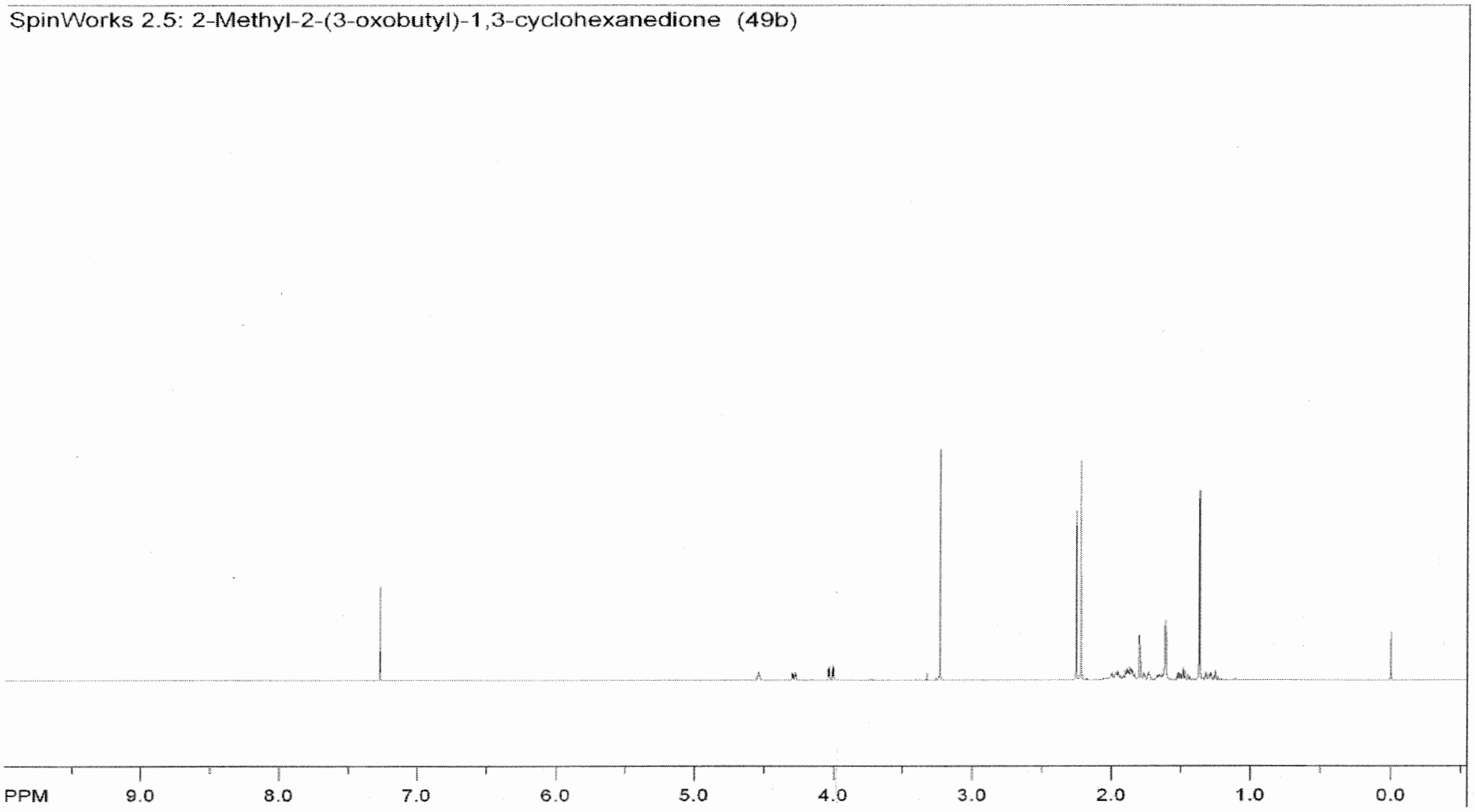

Figure 23. ^{1}H NMR Spectrum of 2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione **(49b)**.

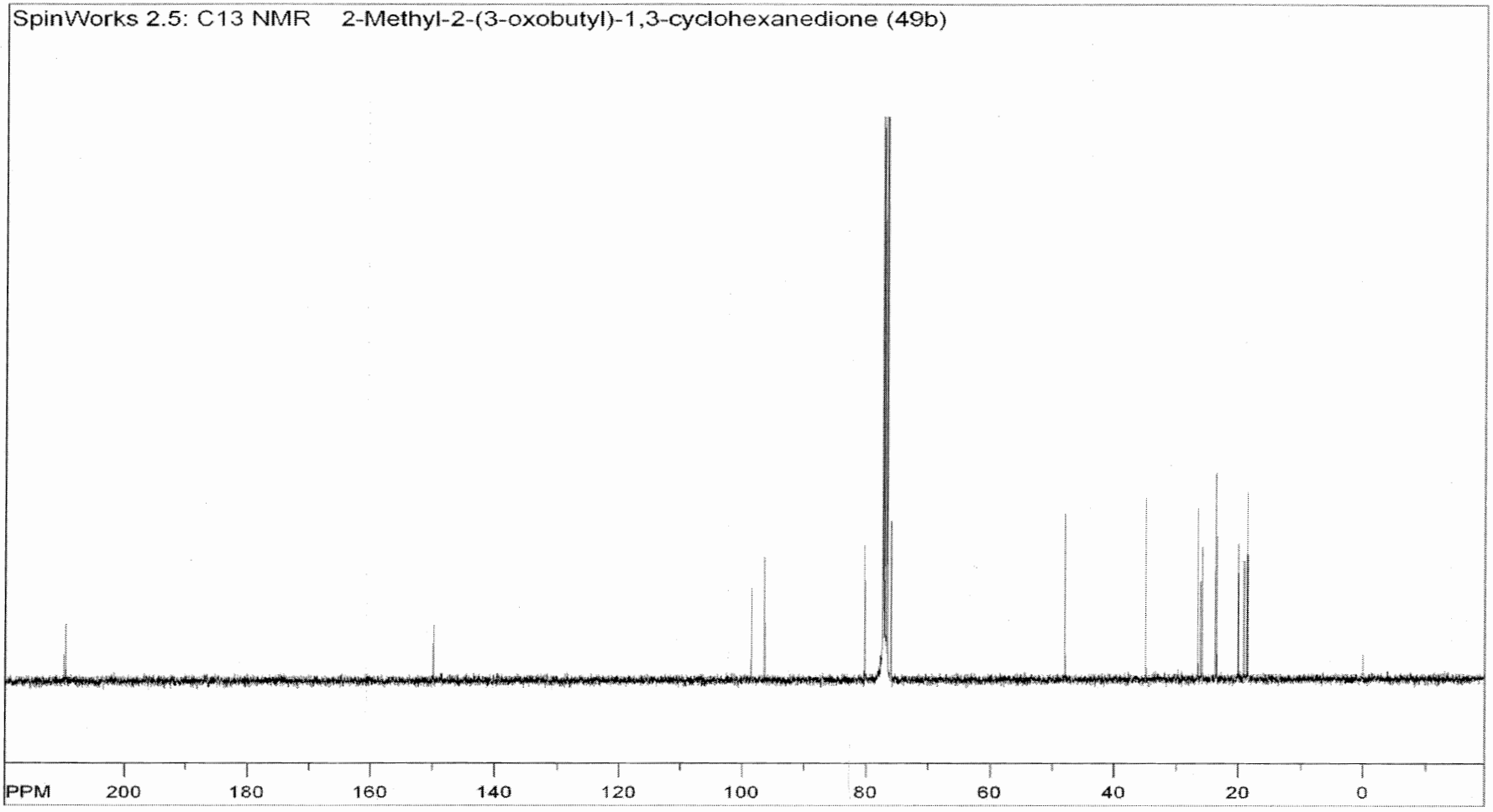

Figure 24. ^{13}C NMR Spectrum of 2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione **(49b)**.

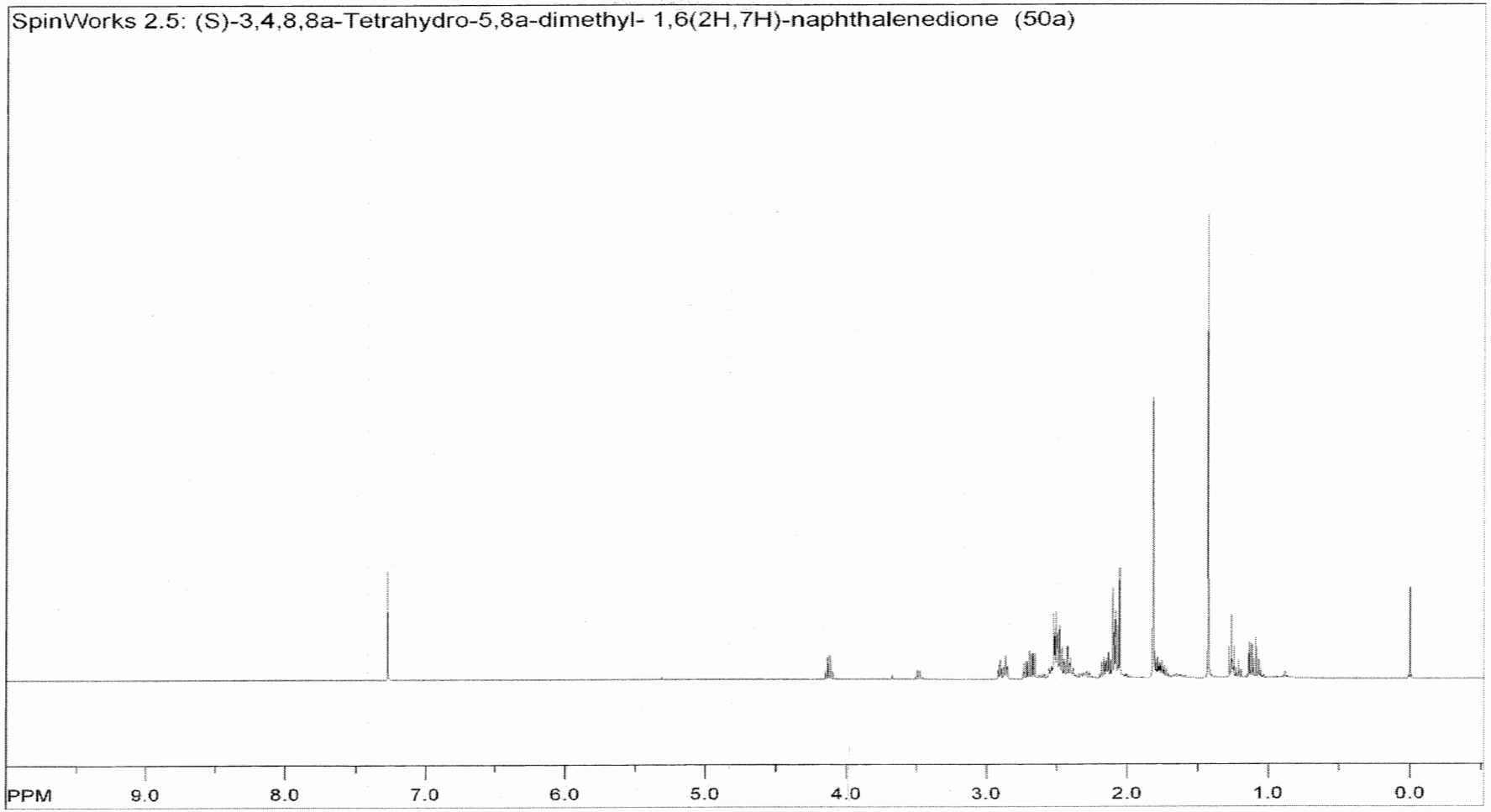

Figure 25. ^{1}H NMR Spectrum of *(S)*-3,4,8,8a-Tetrahydro-5,8a-dimethyl-1,6(2*H*,7*H*)-naphthalenedione **(50a)**.

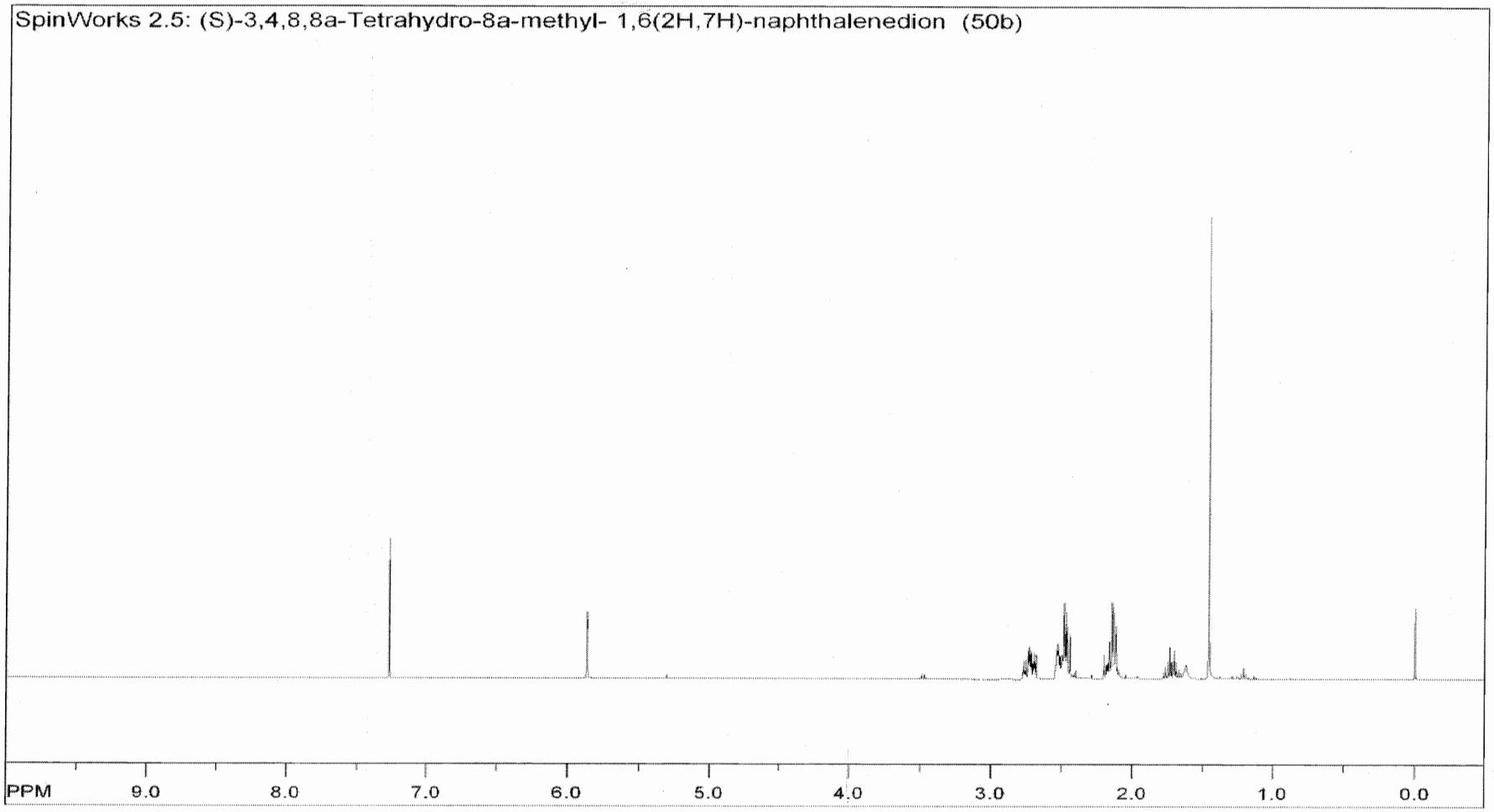

Figure 26. ^{1}H NMR Spectrum of *(S)*-3,4,8,8a-Tetrahydro-8a-methyl-1,6(2*H*,7*H*)-naphthalenedione **(50b)**.

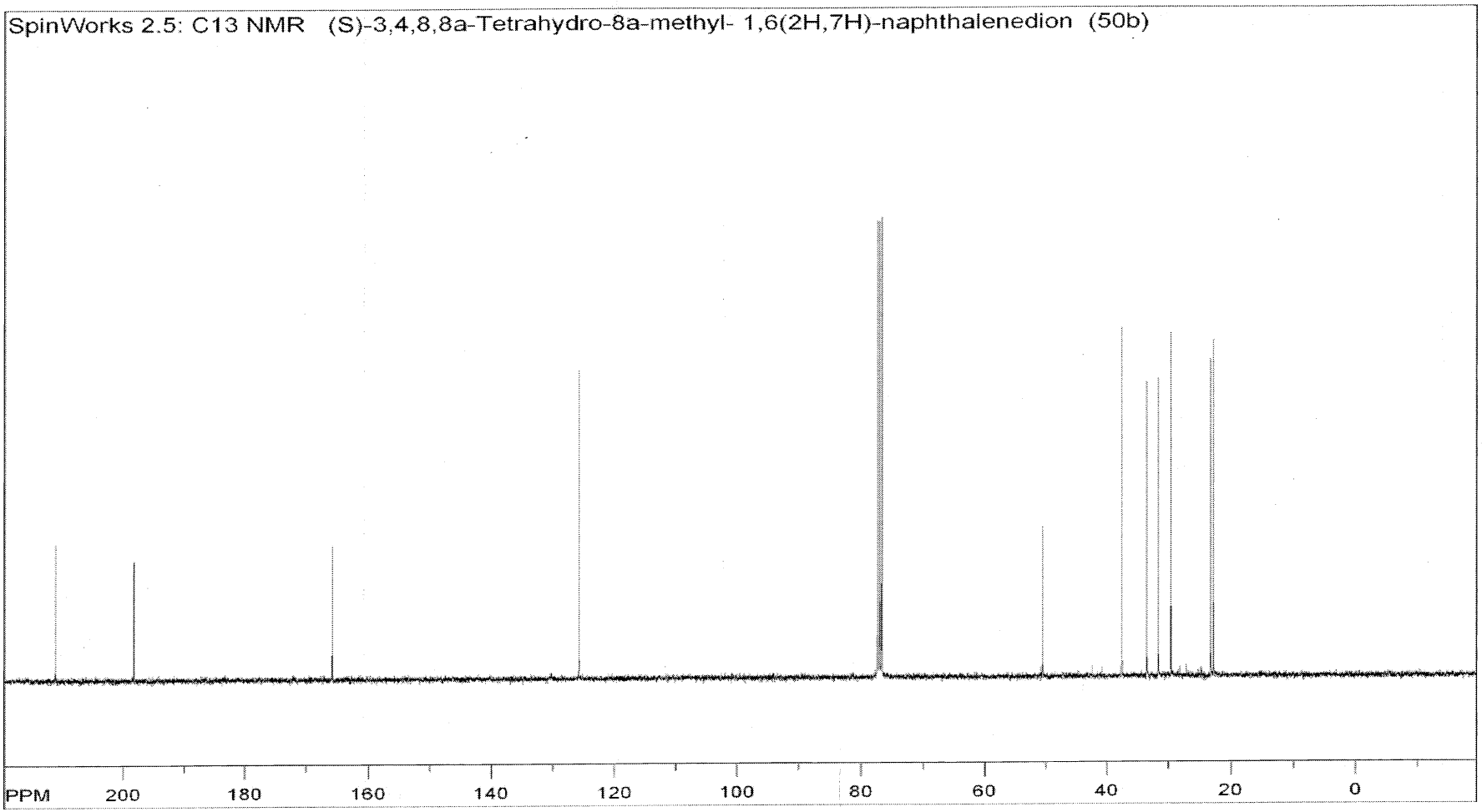

Figure 27. ^{13}C NMR Spectrum of *(S)*-3,4,8,8a-Tetrahydro-8a-methyl-1,6(2*H*,7*H*)-naphthalenedione **(50b)**.

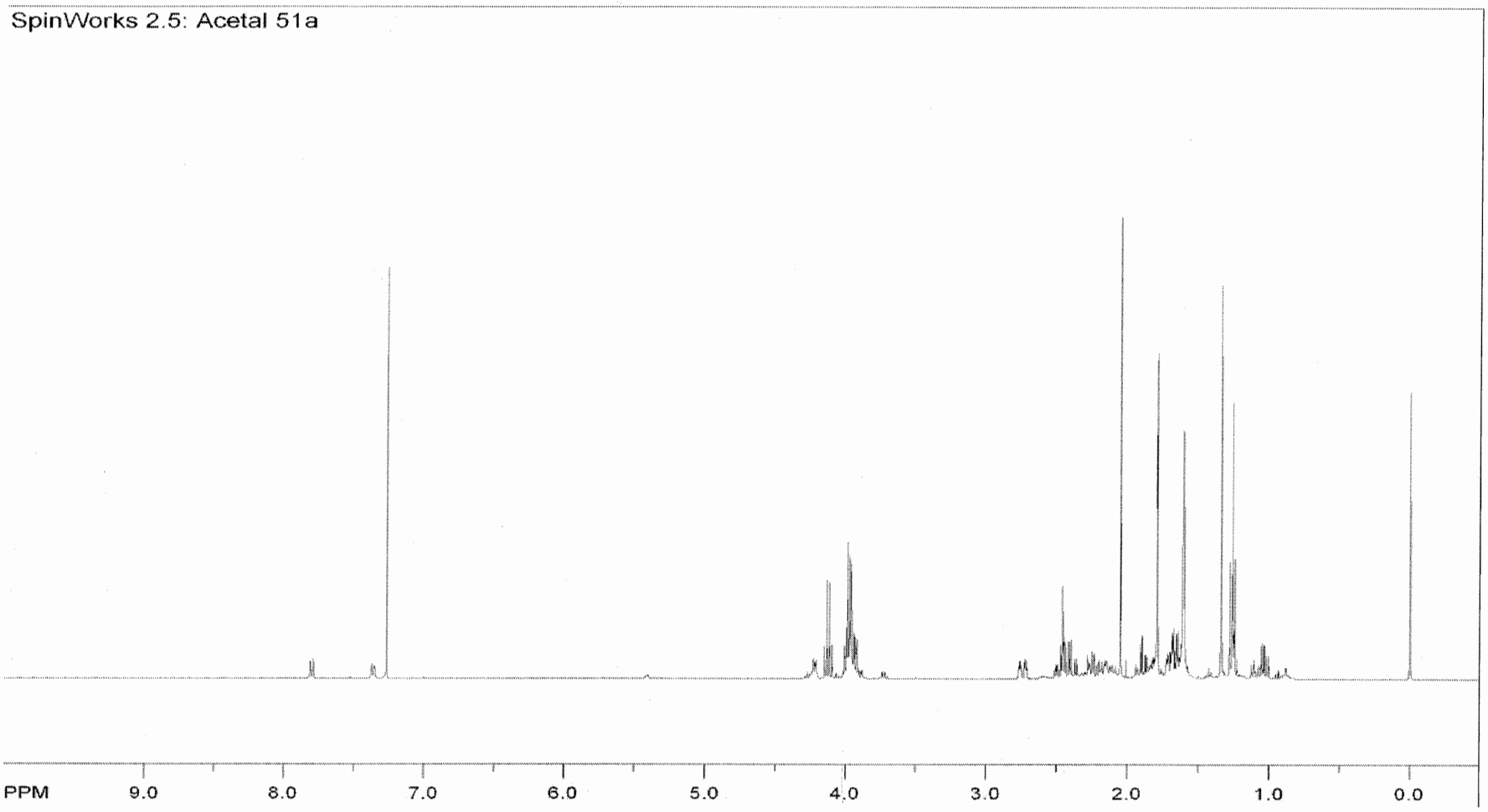

Figure 28. ^{1}H NMR Spectrum of *(S)*-3',4',8',8'a-Tetrahydro-5',8'a-dimethylspiro[1,3-dioxolane-2,1'(2'*H*)-naphthalen]-6'(7'*H*)-one **(51a)**

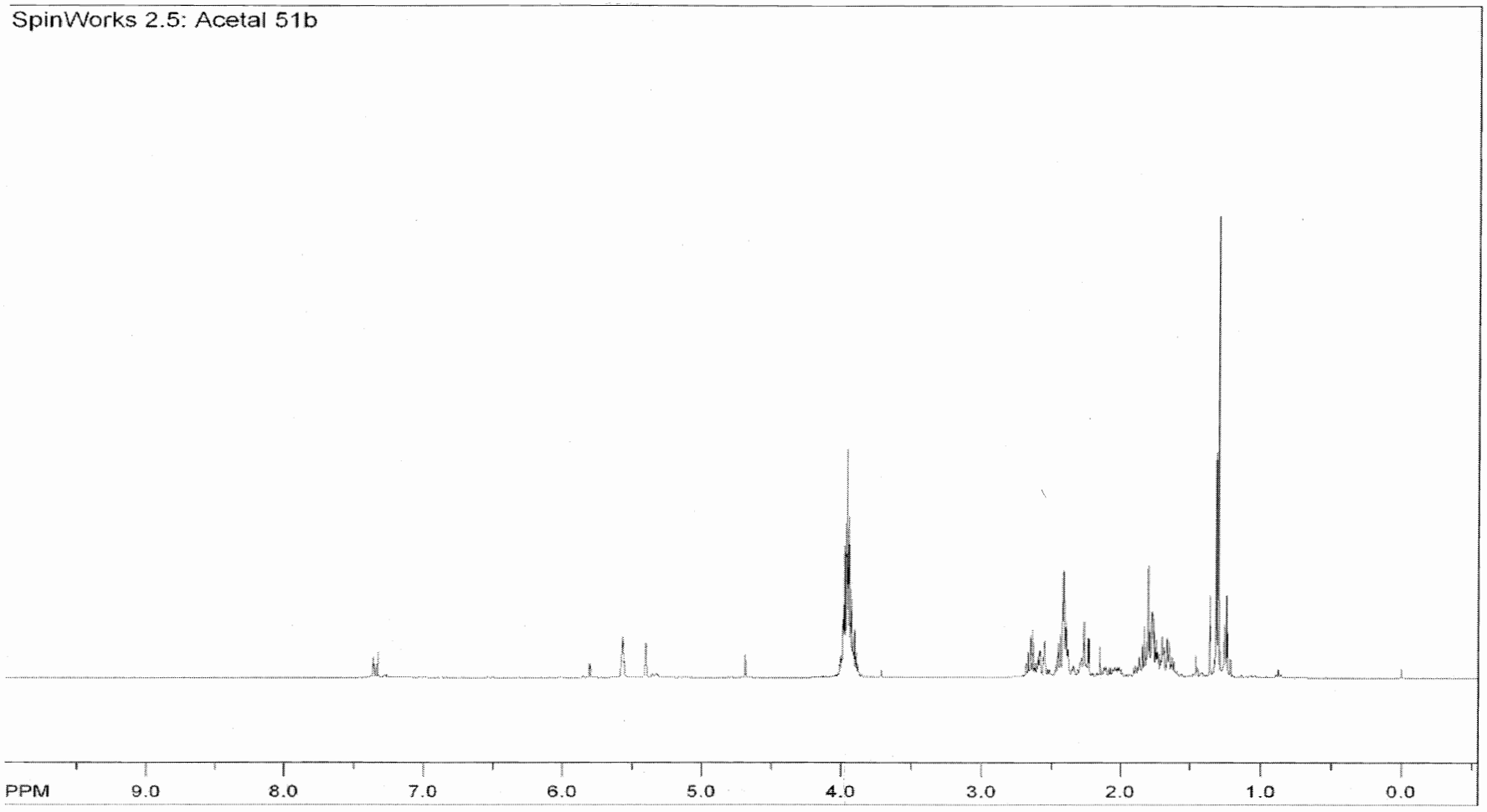

Figure 29. ^{1}H NMR Spectrum of *(S)*-3',4',8',8'a-Tetrahydro-8'a-methylspiro[1,3-dioxolane-2,1'(2'*H*)-naphthalen]-6'(7'*H*)-one **(51b)**.

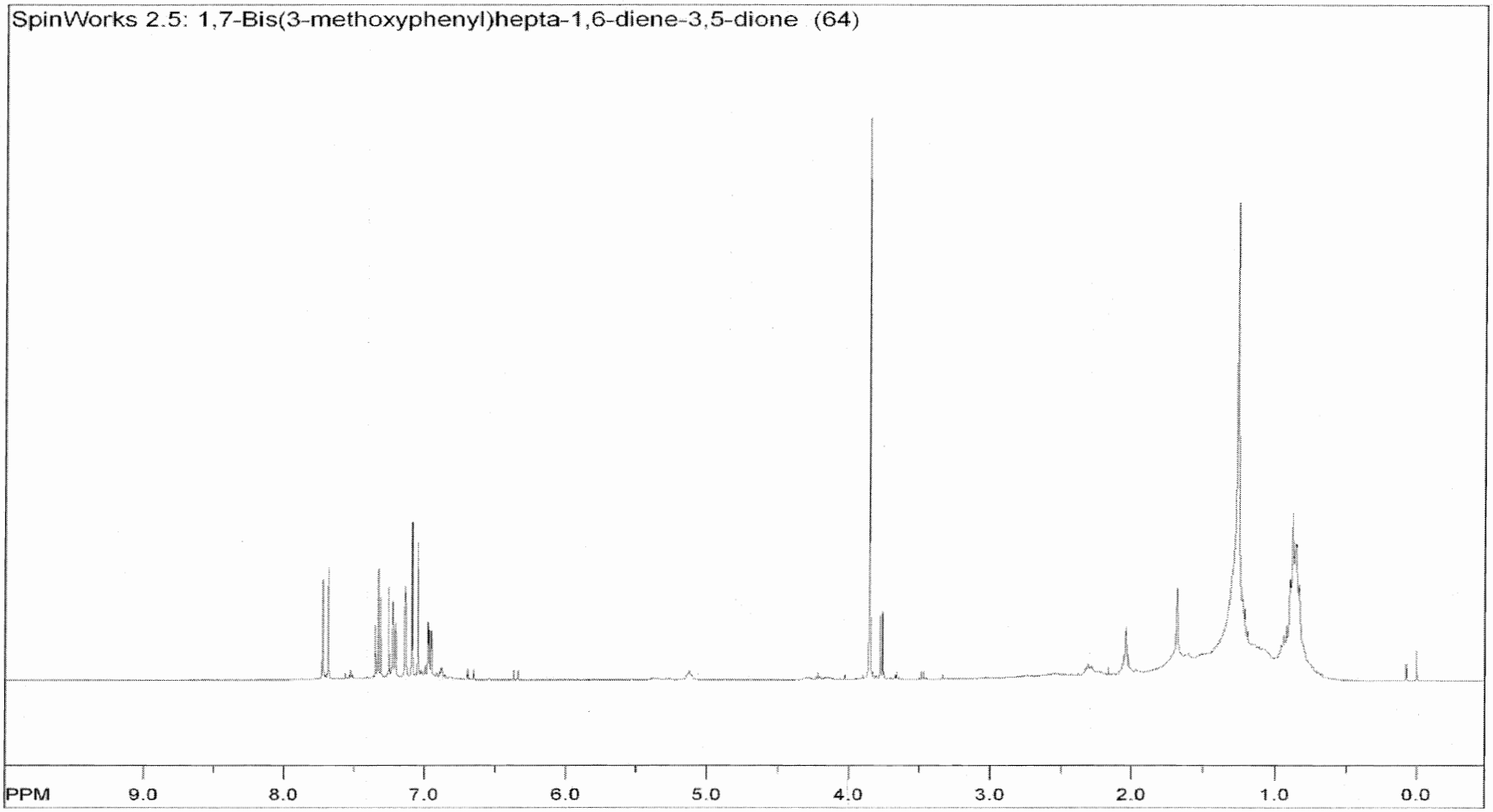

Figure 30. ^{1}H NMR Spectrum of 1,7-Di(3-methoxyphenyl)hepta-1,6-diene-3,5-dione **(64)**.

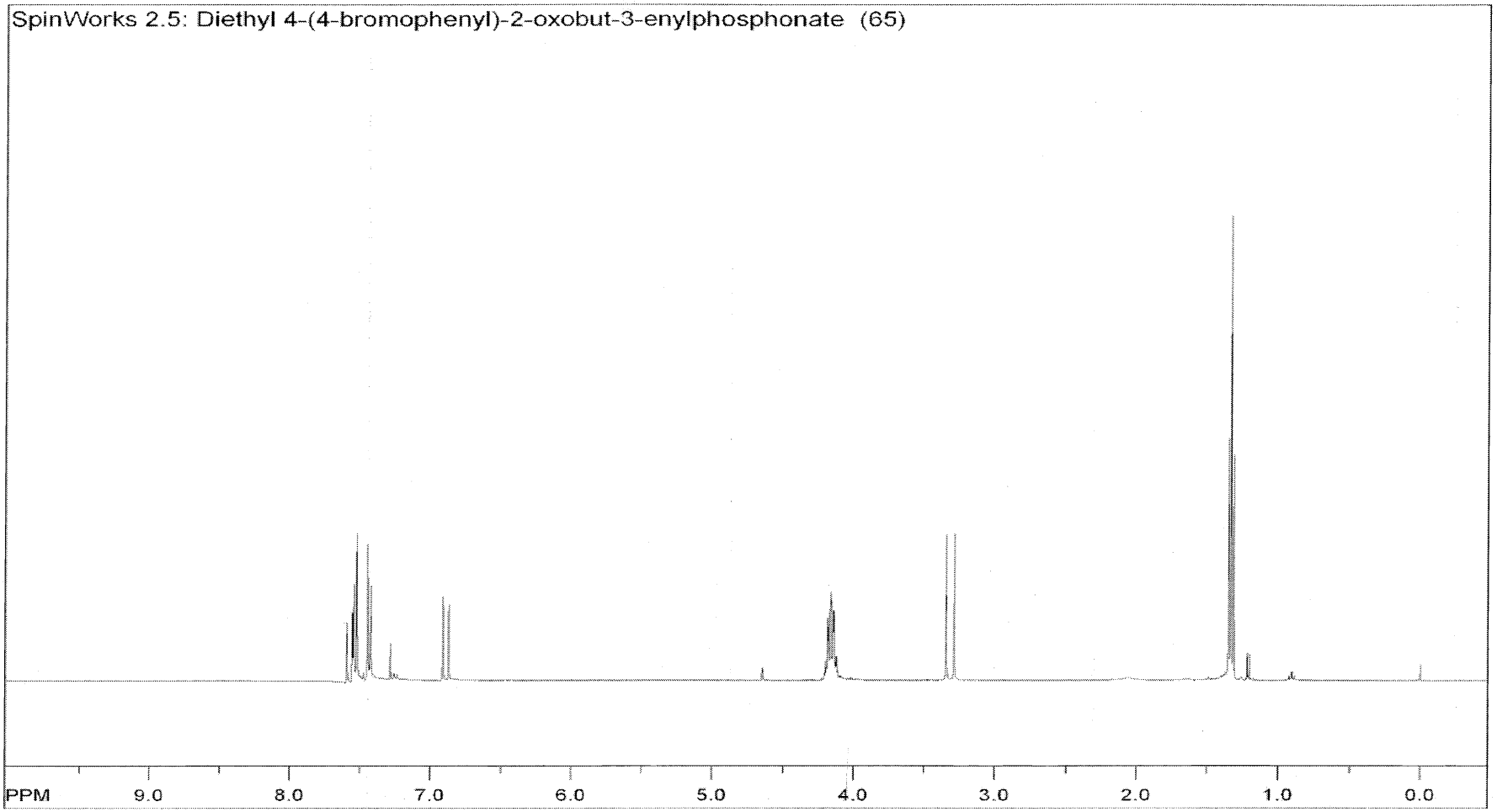

Figure 31. ^{1}H NMR Spectrum of Diethyl 4-(4-bromophenyl)-2-oxobut-3-enylphosphonate **(65)**.

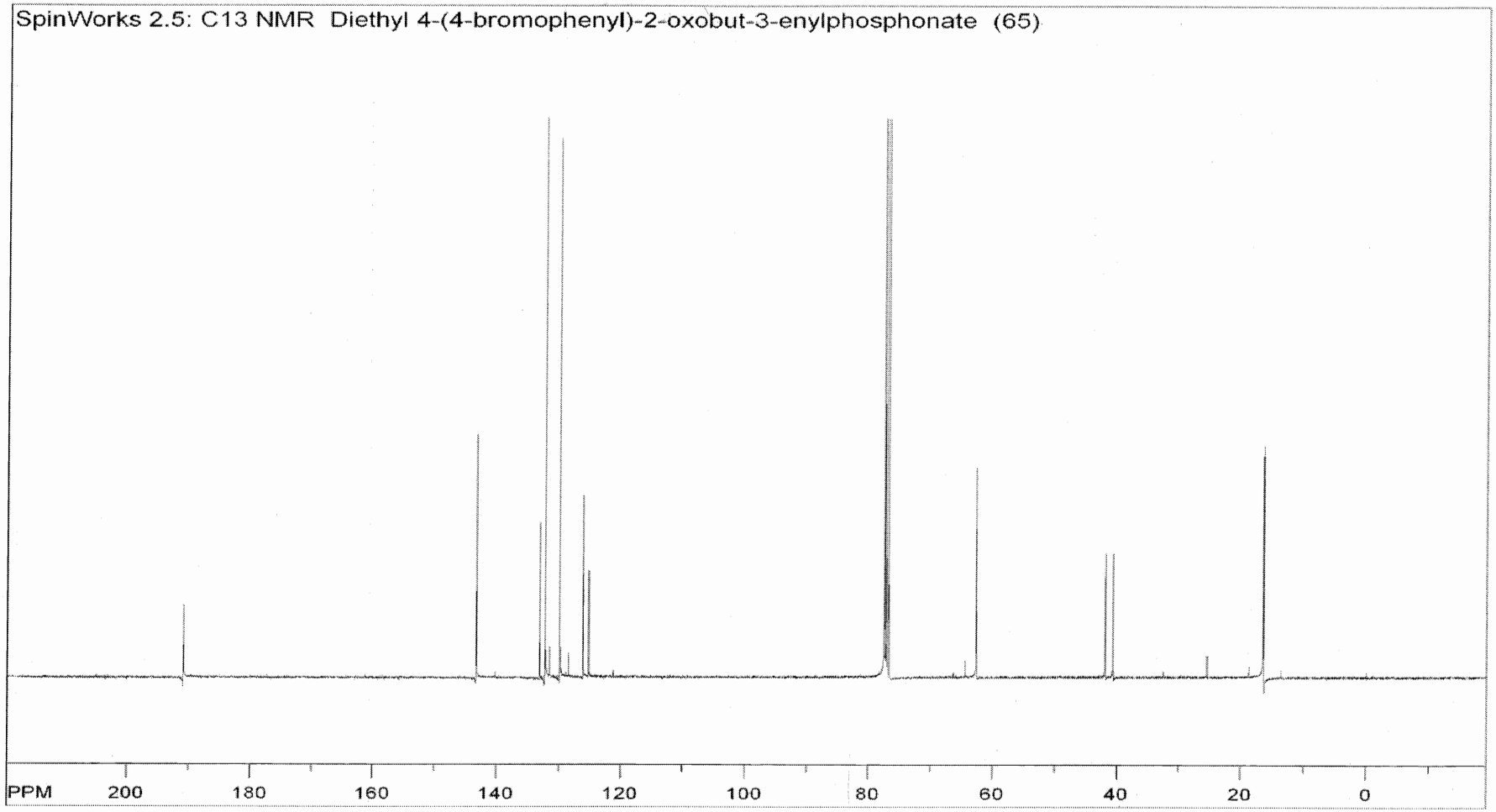

Figure 32. ^{13}C NMR Spectrum of Diethyl 4-(4-bromophenyl)-2-oxobut-3-enylphosphonate **(65)**.

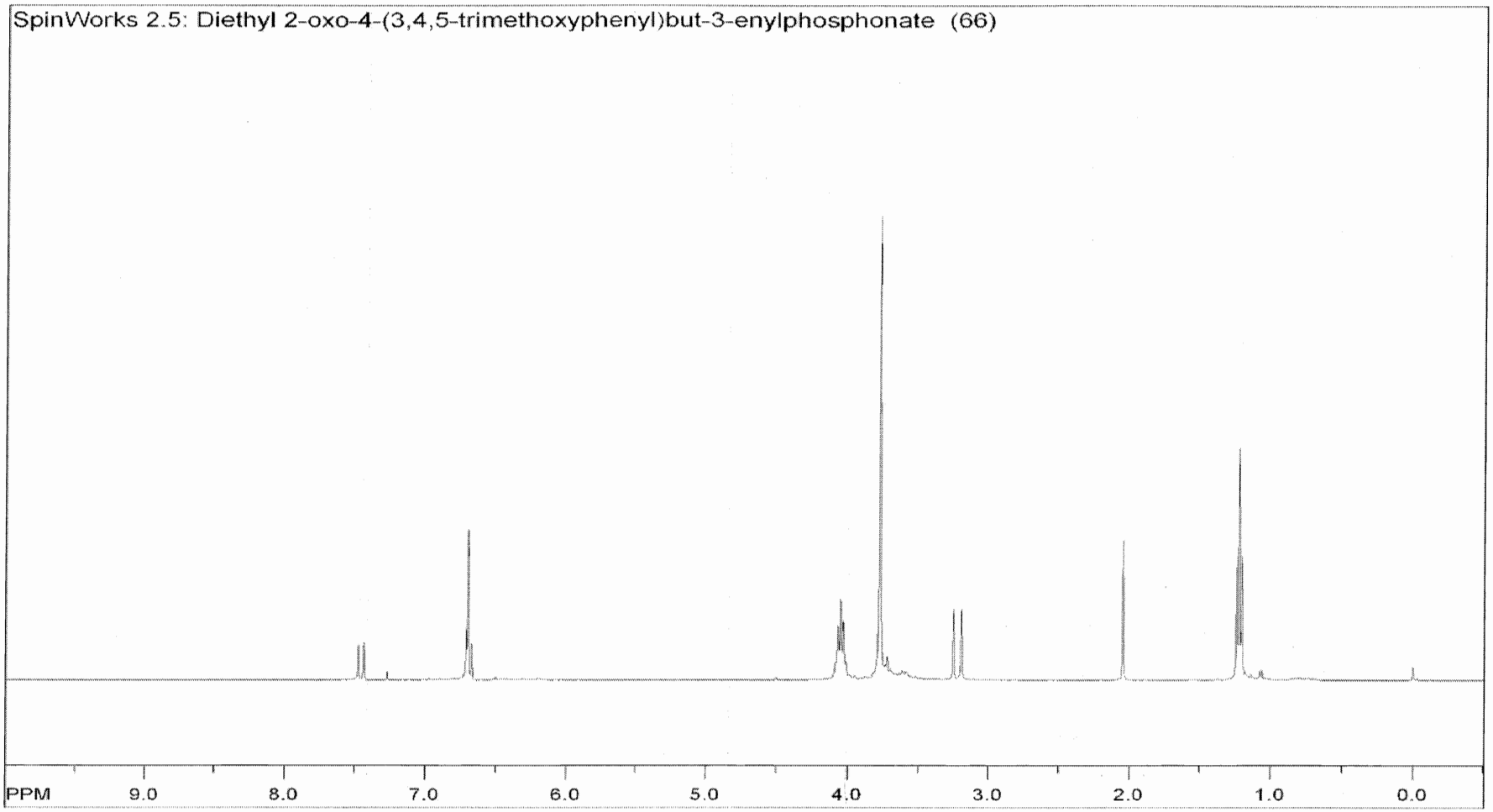

Figure 33. ^{1}H NMR Spectrum of Diethyl 4-(3,4,5-trimethoxyphenyl)-2-oxo-but-3-enylphosphonate **(66)**.

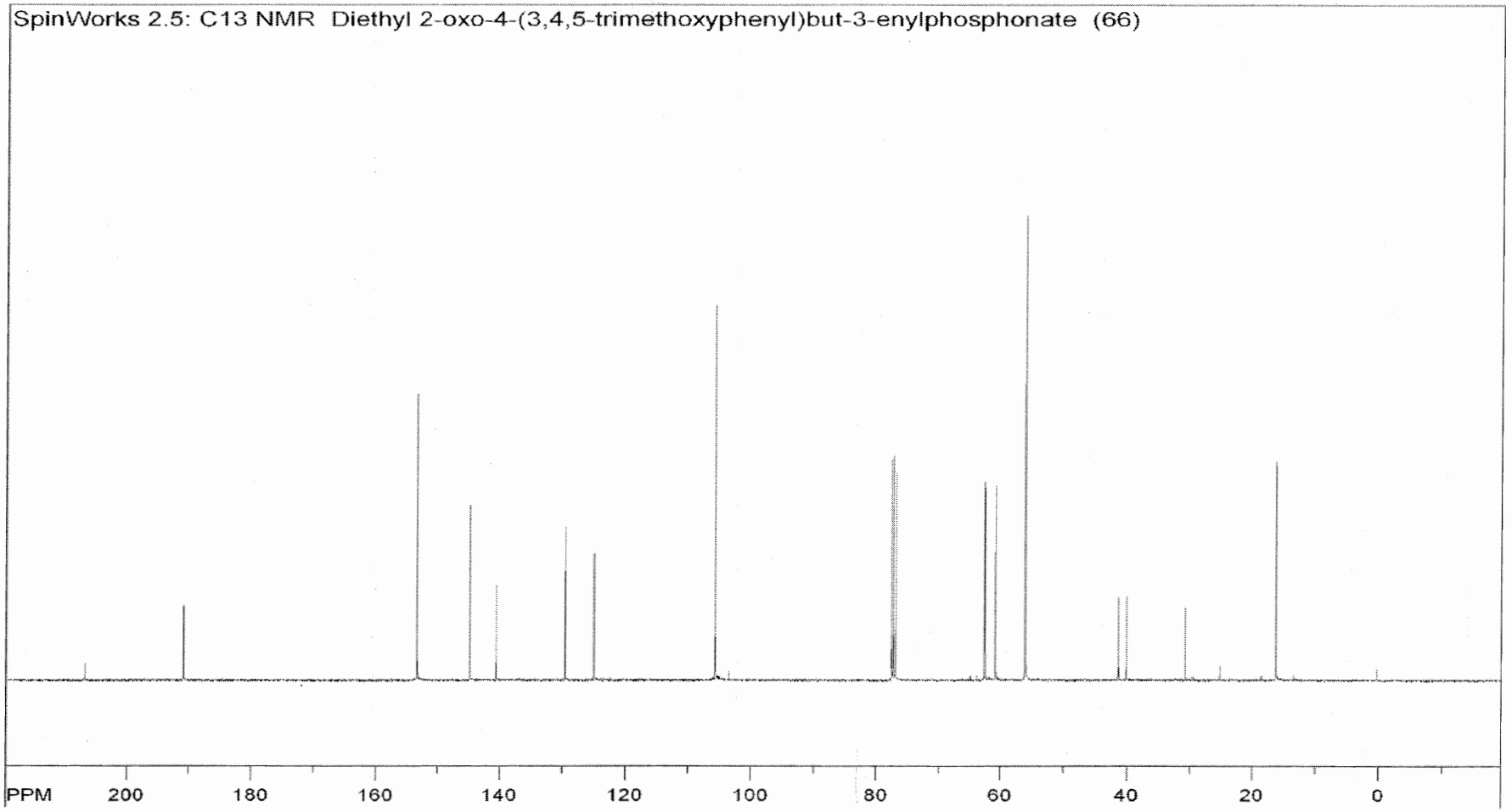

Figure 34. ^{13}C NMR Spectrum of Diethyl 4-(3,4,5-trimethoxyphenyl)-2-oxo-but-3-enylphosphonate **(66)**.

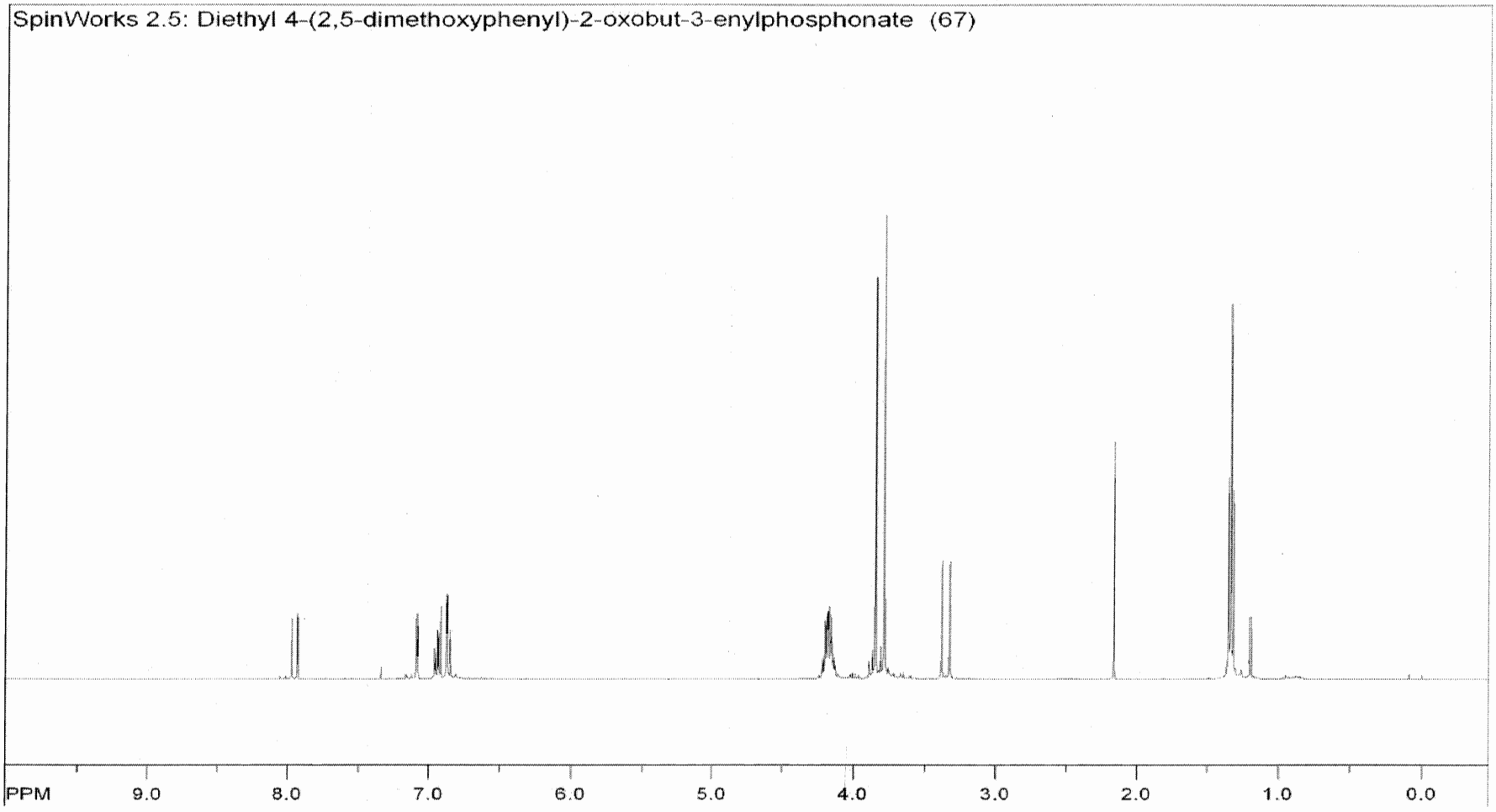

Figure 35. ^{1}H NMR Spectrum of Diethyl 4-(2,5-dimethoxyphenyl)-2-oxobut-3-enylphosphonate **(67)**.

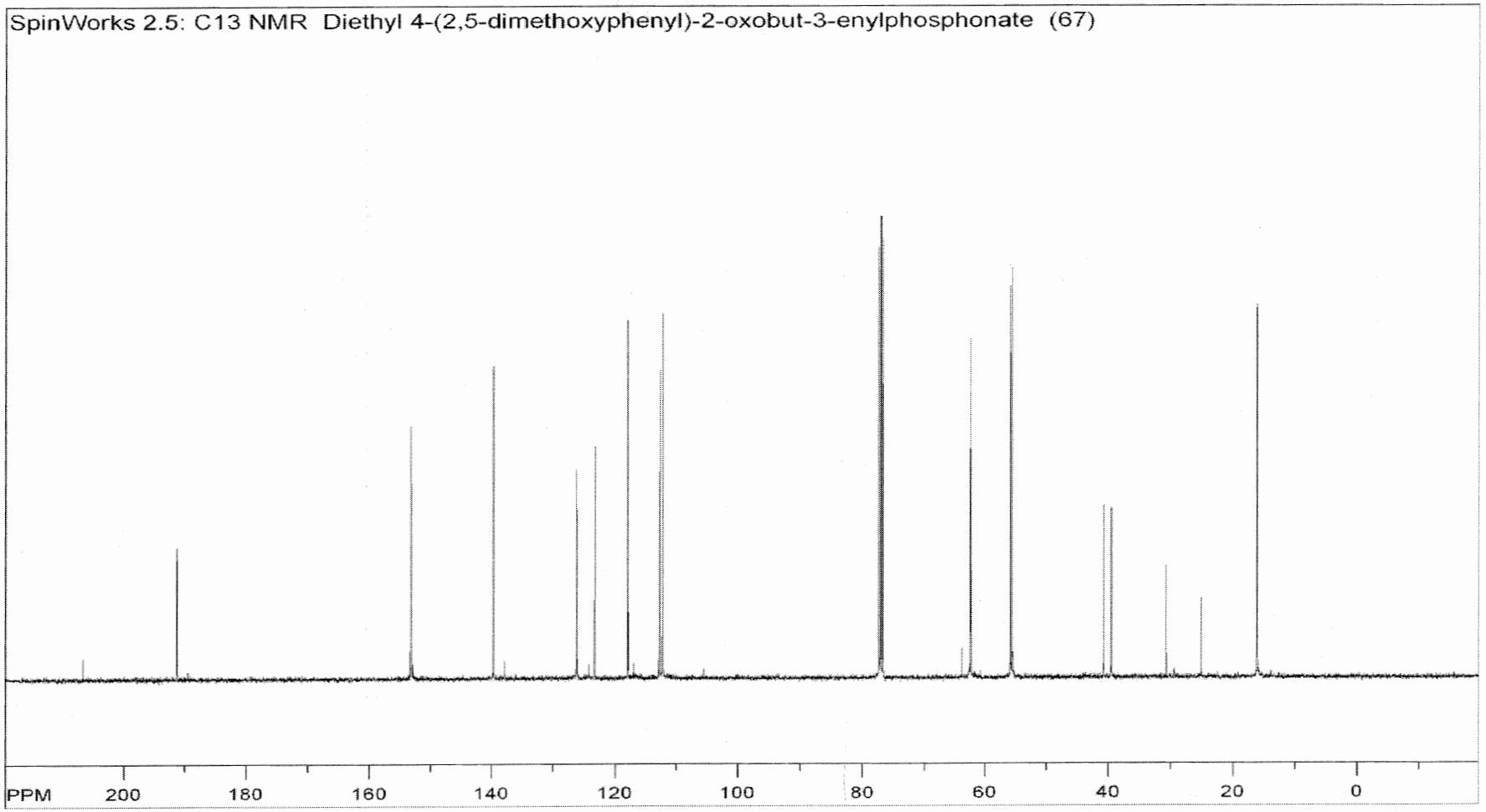

Figure 36. ^{13}C NMR Spectrum of Diethyl 4-(2,5-dimethoxyphenyl)-2-oxobut-3-enylphosphonate **(67)**.

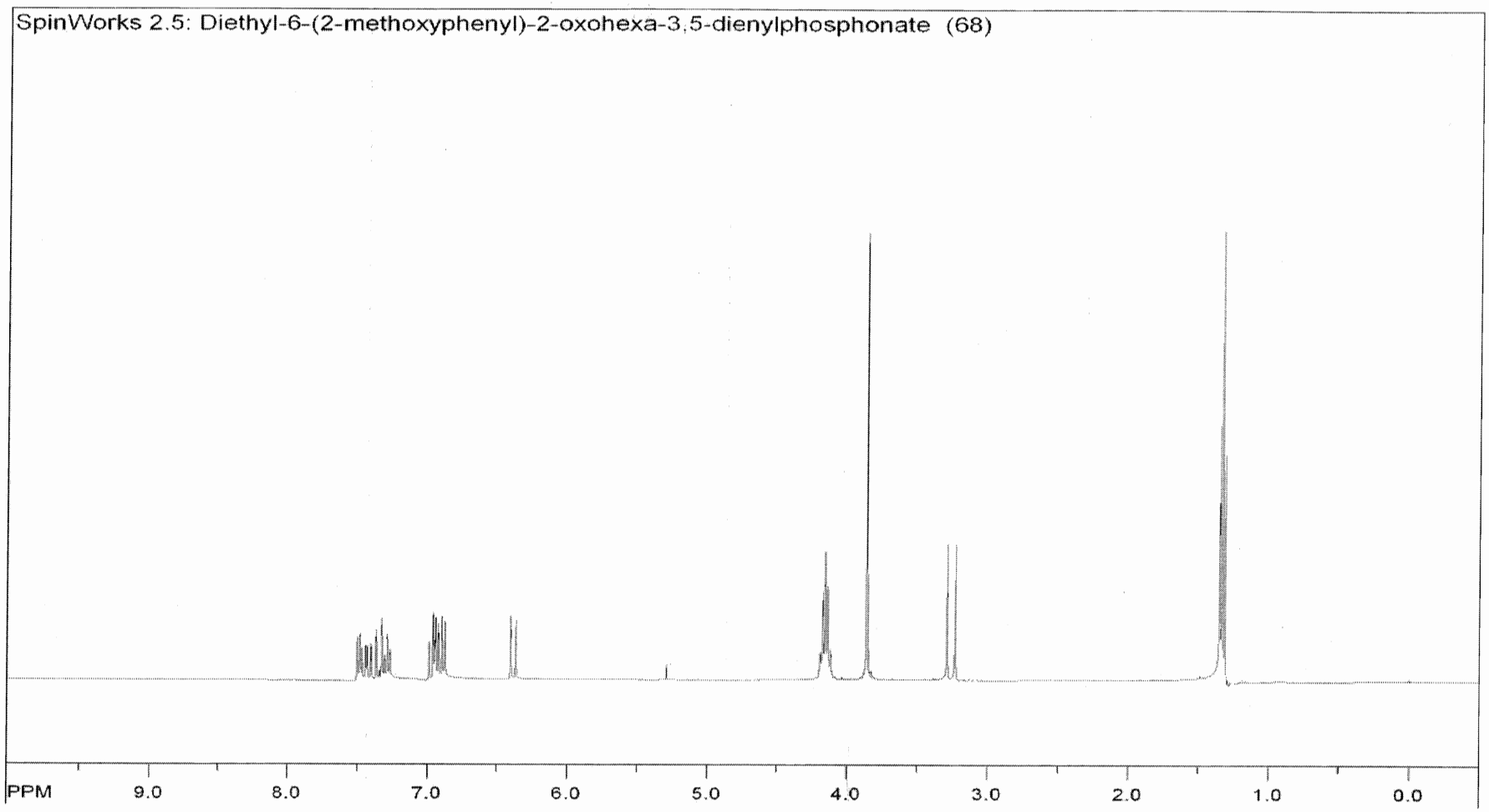

Figure 37. ^{1}H NMR Spectrum of Diethyl 6-(2-methoxyphenyl)-2-oxohexa-3,5-dienylphosphonate **(68)**.

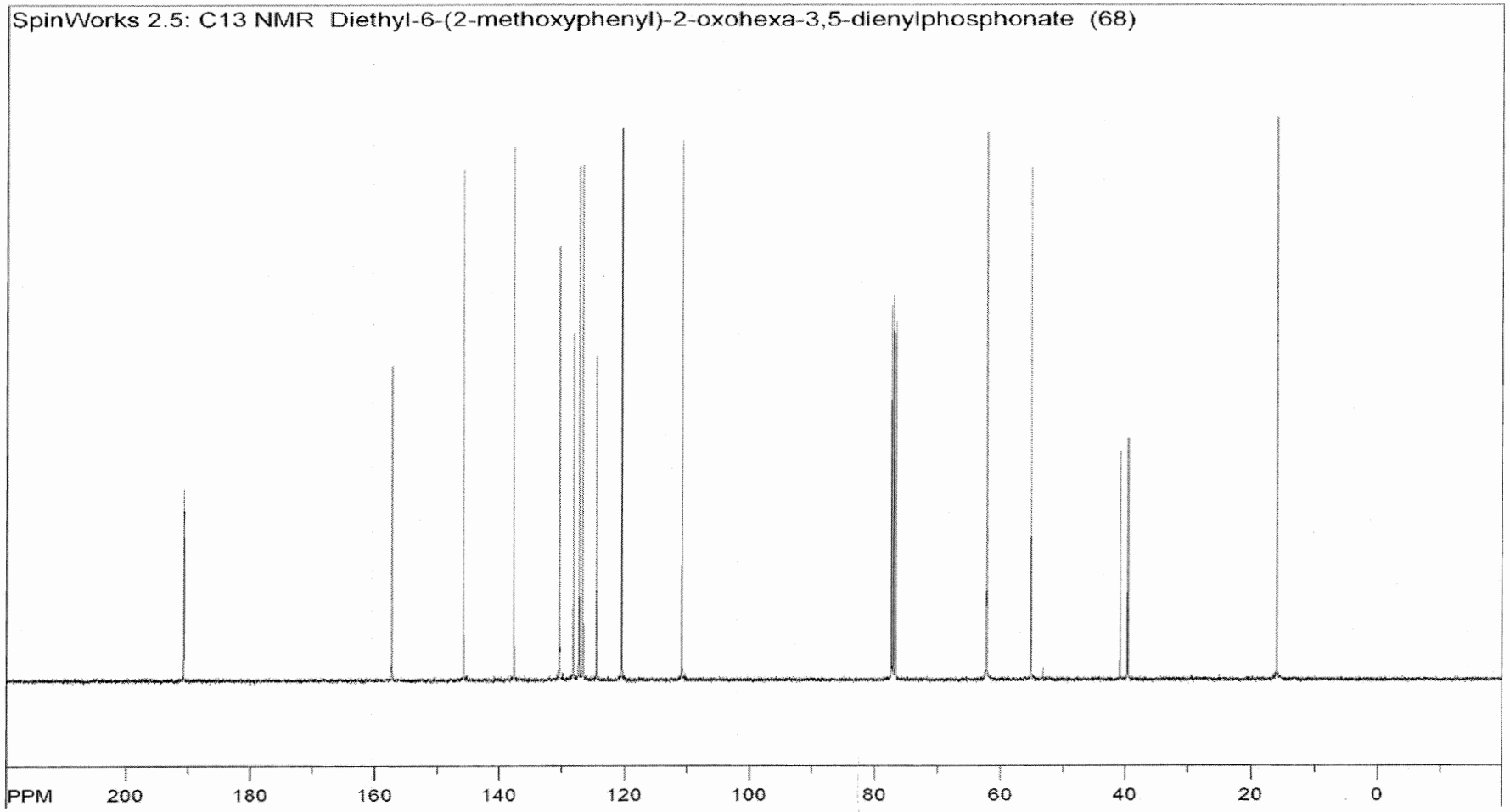

Figure 38. ^{13}C NMR Spectrum of Diethyl 6-(2-methoxyphenyl)-2-oxohexa-3,5-dienylphosphonate **(68)**.

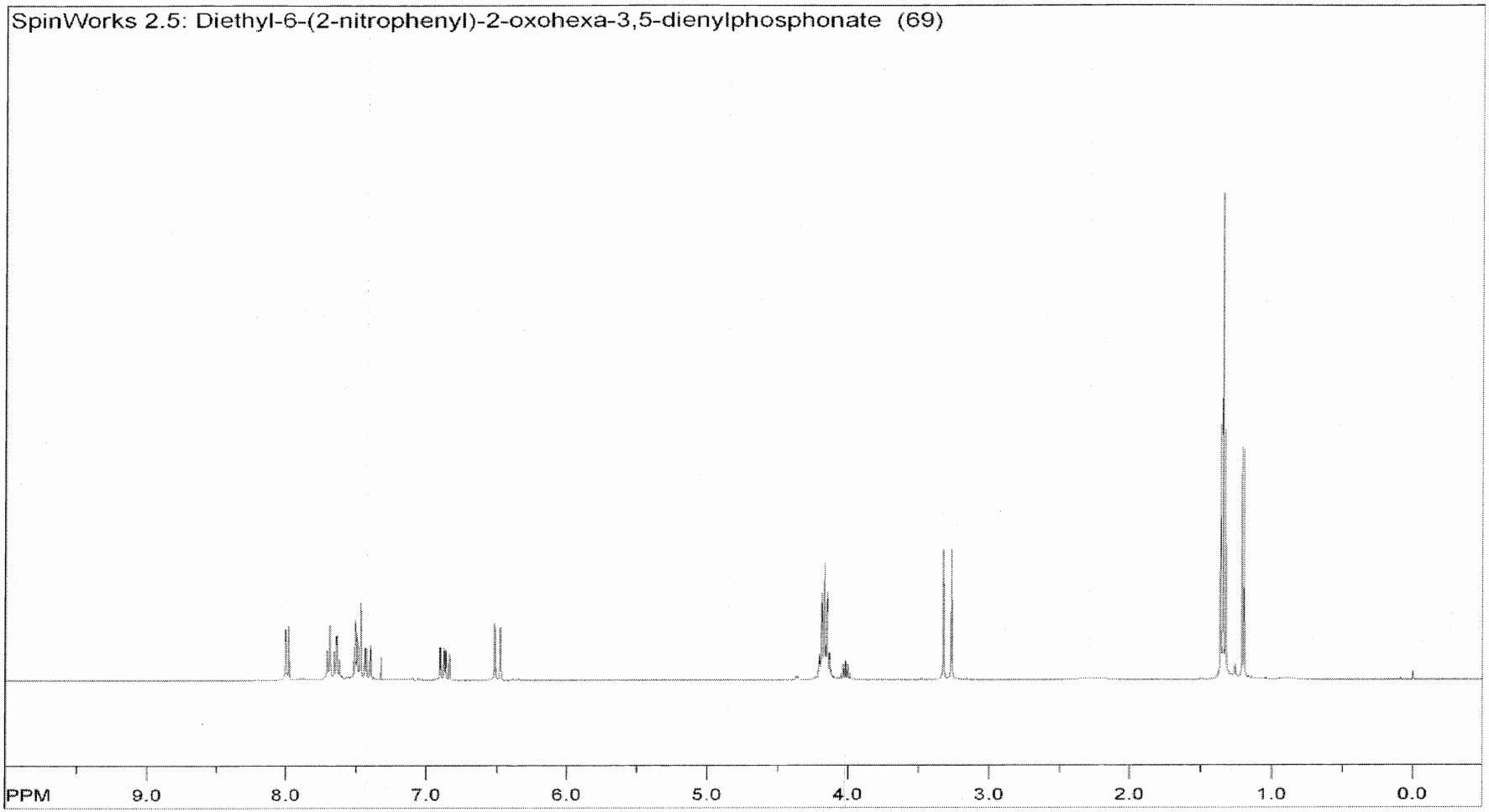

Figure 39. ^{1}H NMR Spectrum of Diethyl 6-(2-nitrophenyl)-2-oxohexa-3,5-dienylphosphonate **(69)**.

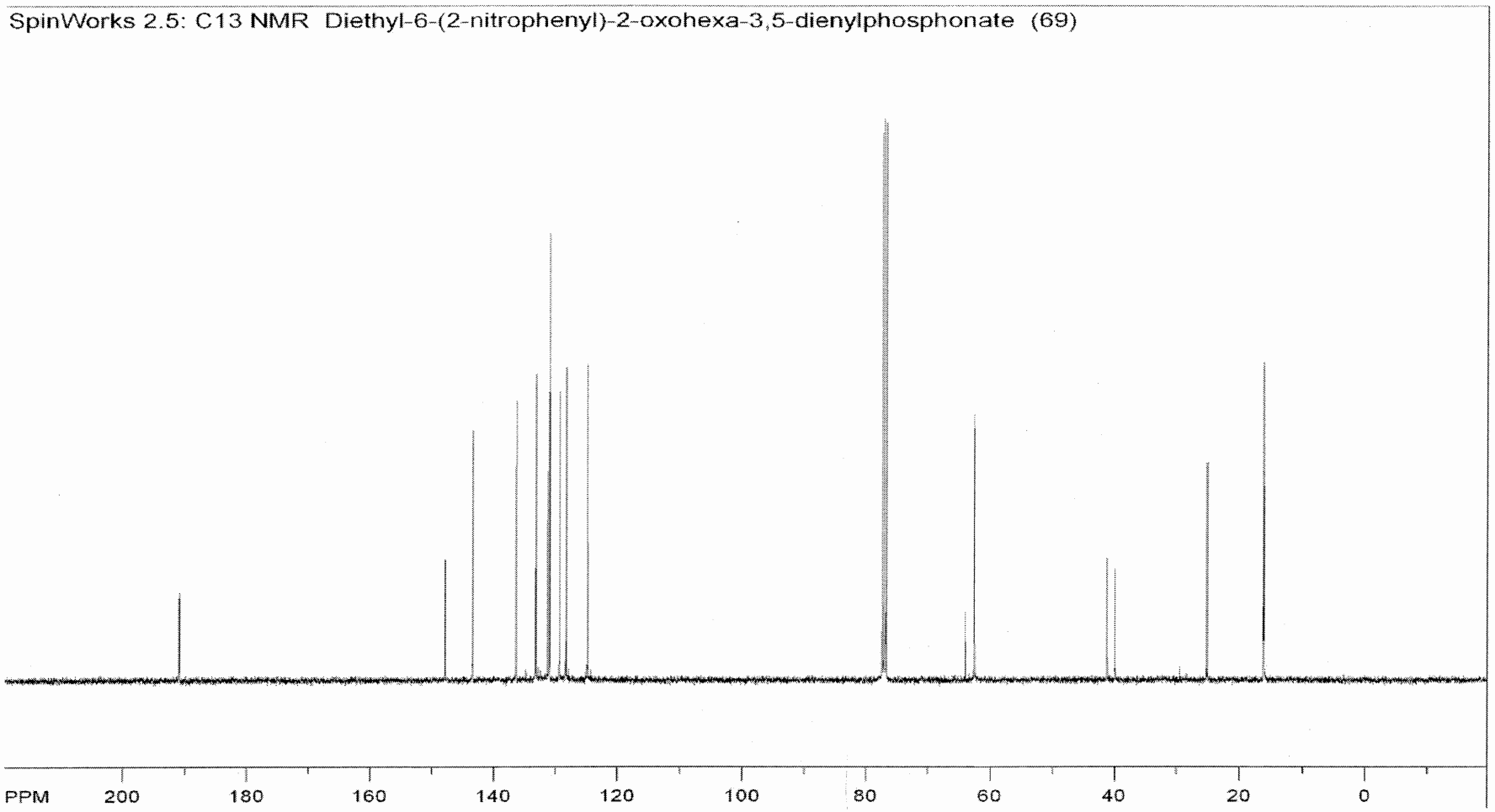

Figure 40. ^{13}C NMR Spectrum of Diethyl 6-(2-nitrophenyl)-2-oxohexa-3,5-dienylphosphonate **(69)**.

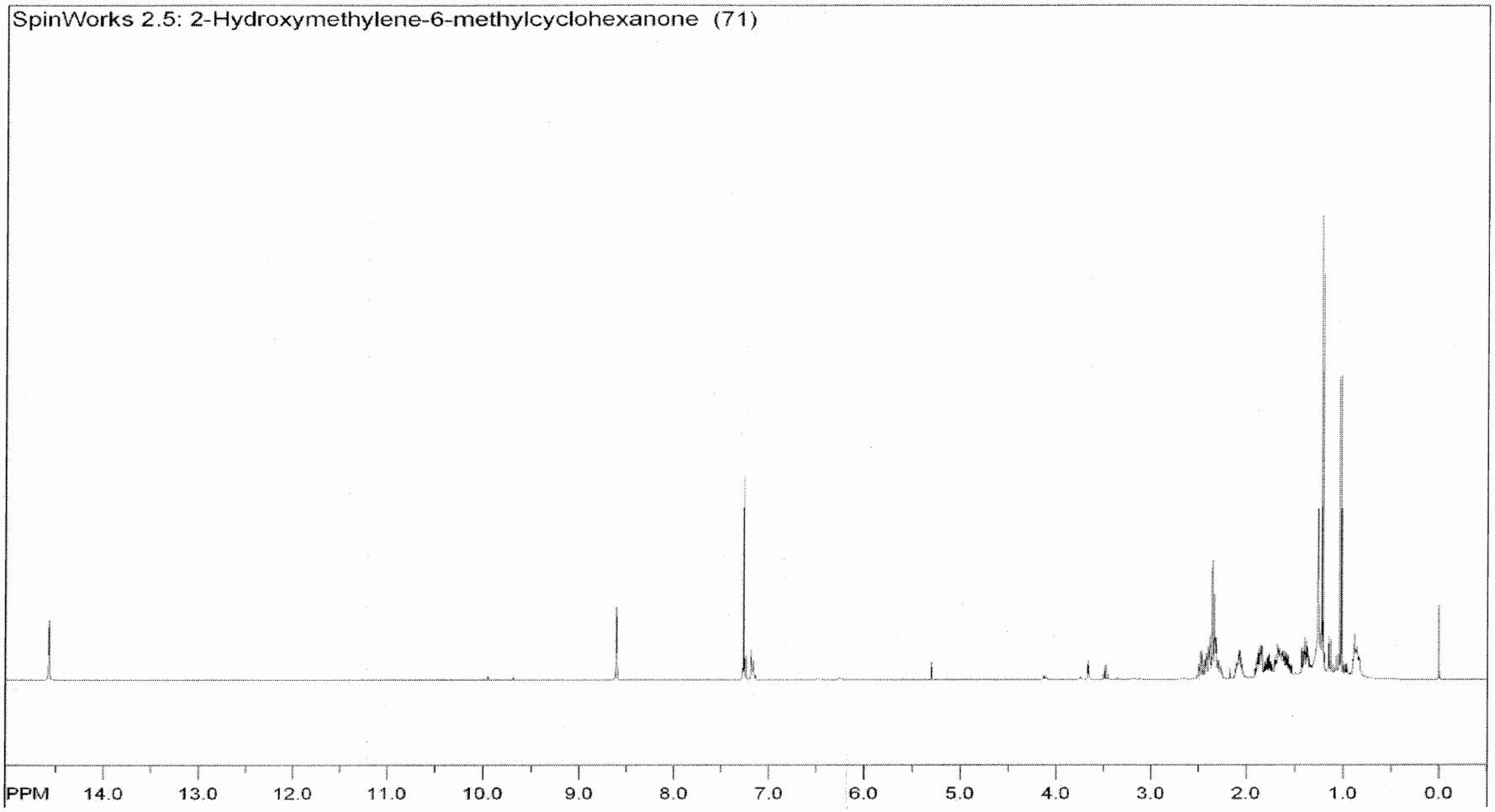

Figure 41. ^{1}H NMR Spectrum of 2-Hydroxymethylene-6-methylcyclohexanone **(71)**.

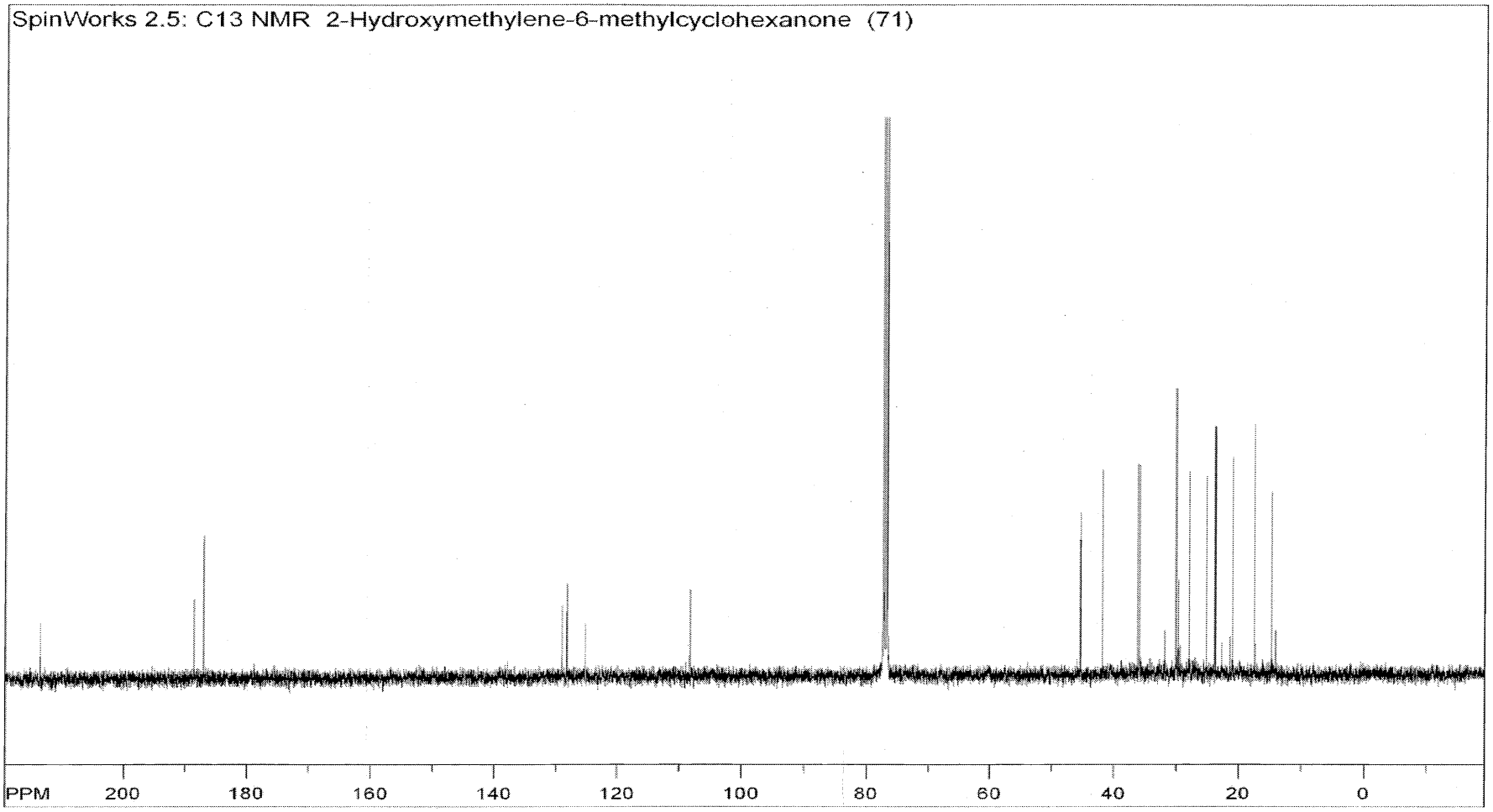

Figure 42. ^{13}C NMR Spectrum of 2-Hydroxymethylene-6-methylcyclohexanone **(71)**.

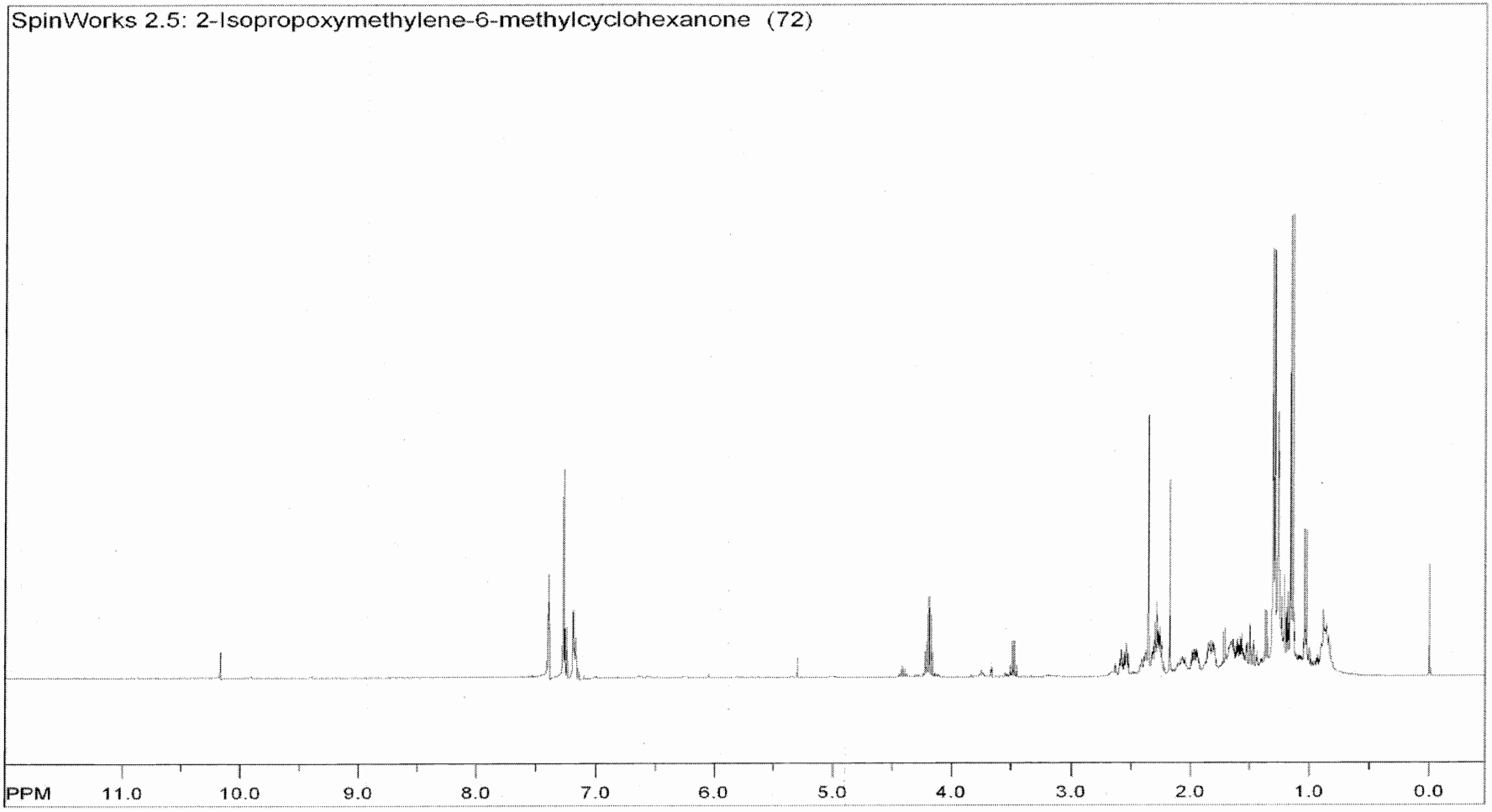

Figure 43. ^{1}H NMR Spectrum of 2-Isopropoxymethylene-6-methylcyclohexanone **(72)**.

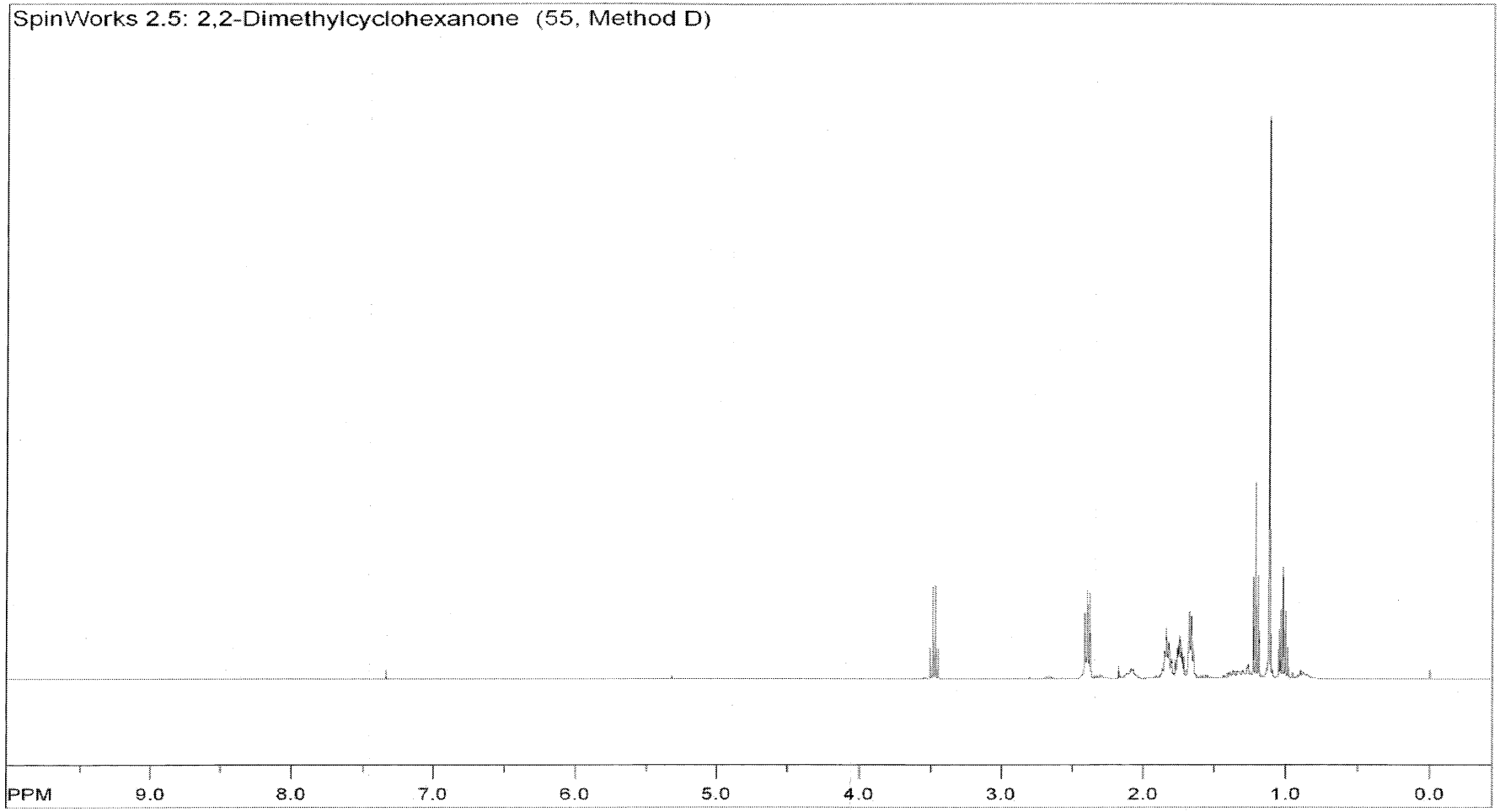

Figure 44. ^{1}H NMR Spectrum of 2,2-Dimethylcyclohexanone **(55)**.

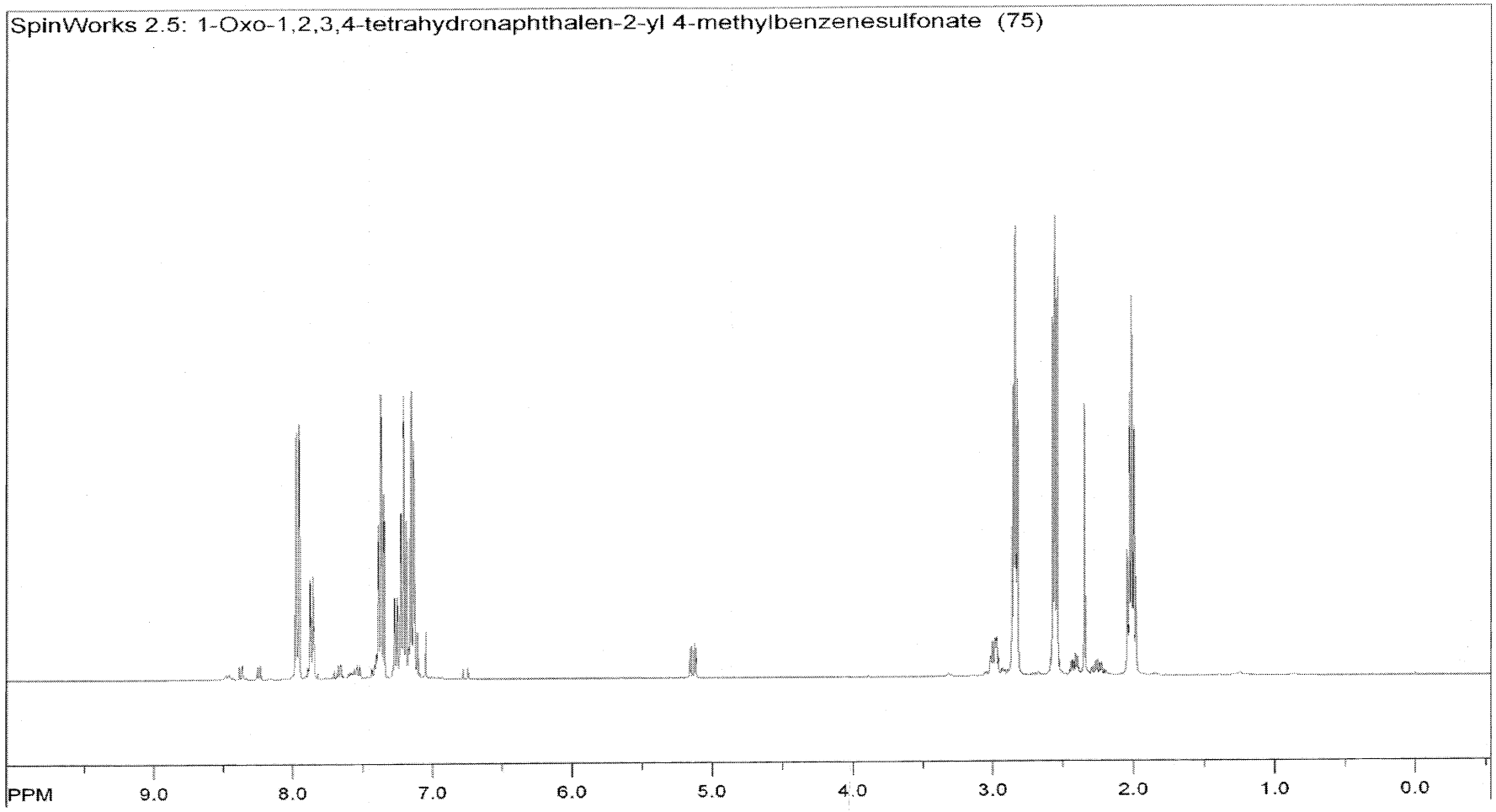

Figure 45. ^{1}H NMR Spectrum of 1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl 4-methylbenzenesulfonate **(75)**.

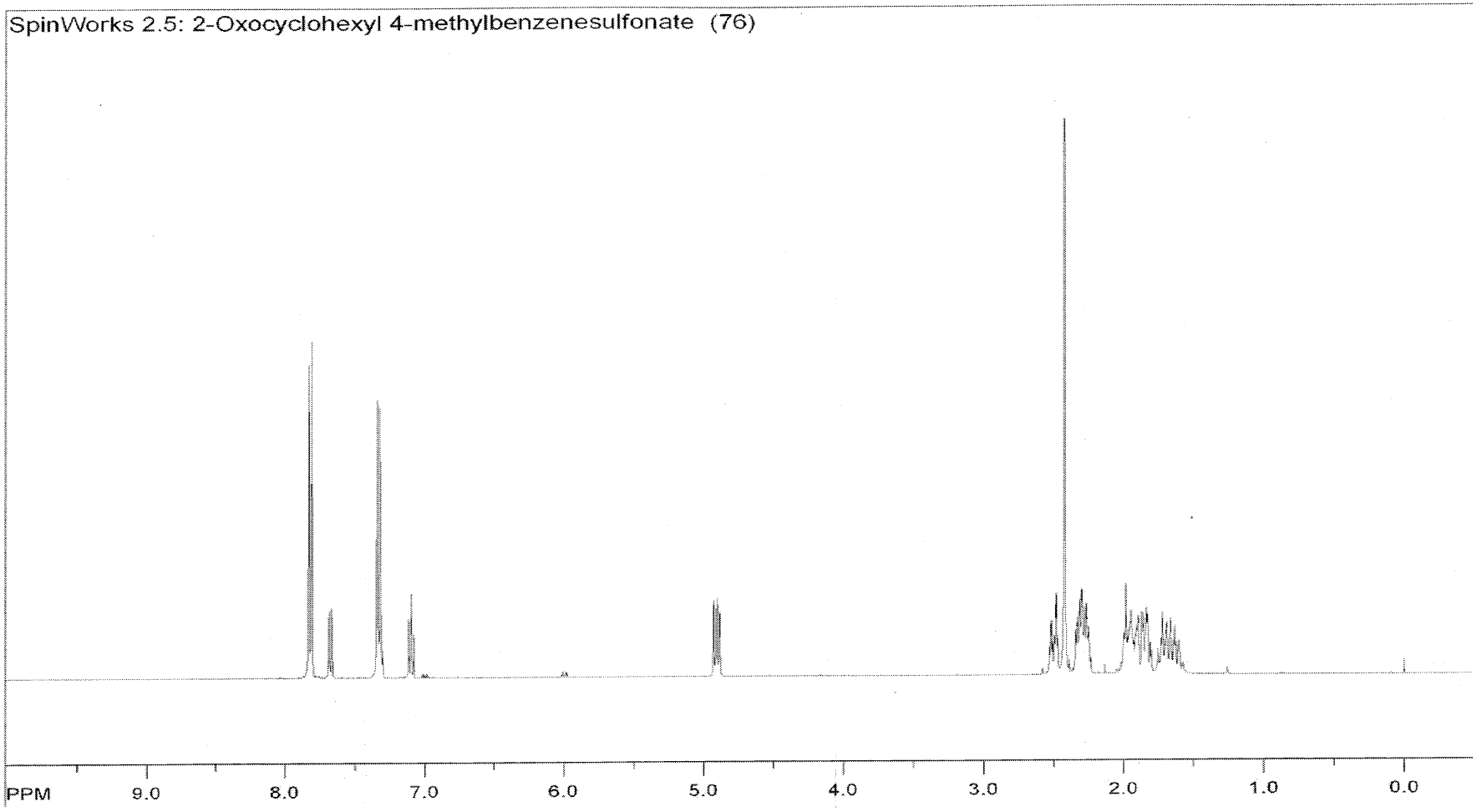

Figure 46. ^{1}H NMR Spectrum of 2-Oxocyclohexyl 4-methylbenzenesulfonate **(76)**.

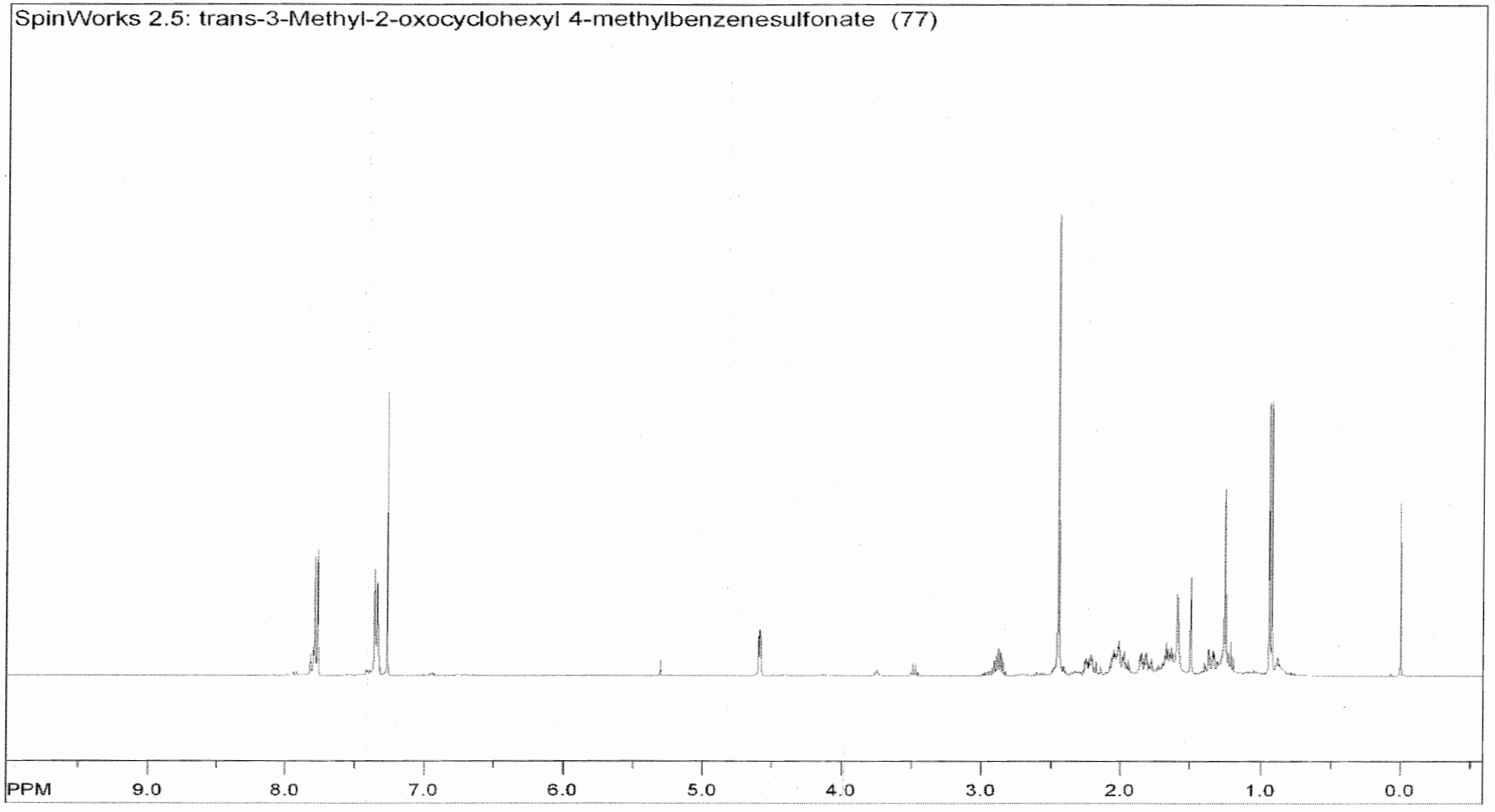

Figure 47. ^{1}H NMR Spectrum of *trans*-3-Methyl-2-oxocyclohexyl 4-methylbenzenesulfonate **(77)**.

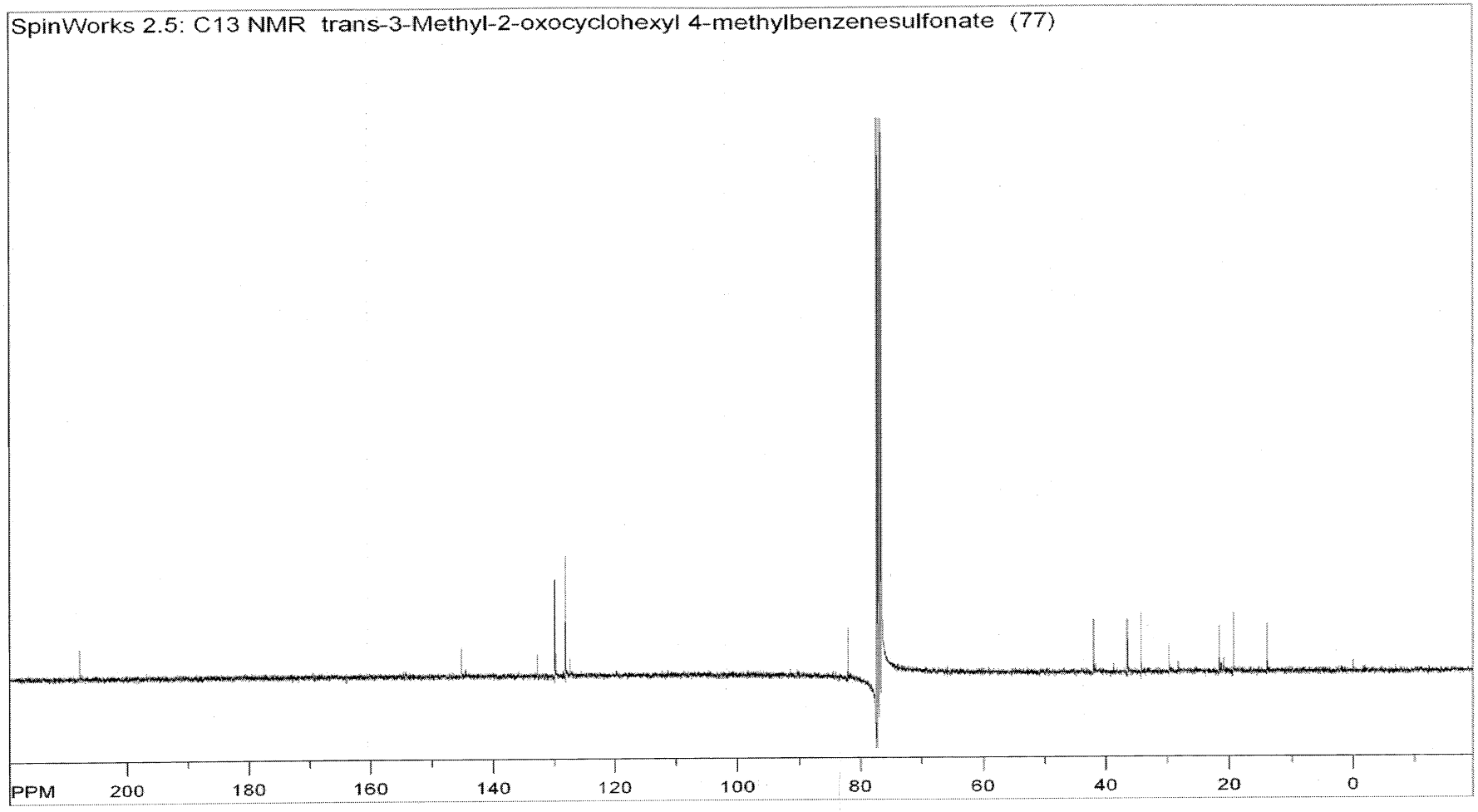

Figure 48. ^{13}C NMR Spectrum of *trans*-3-Methyl-2-oxocyclohexyl 4-methylbenzenesulfonate **(77)**.

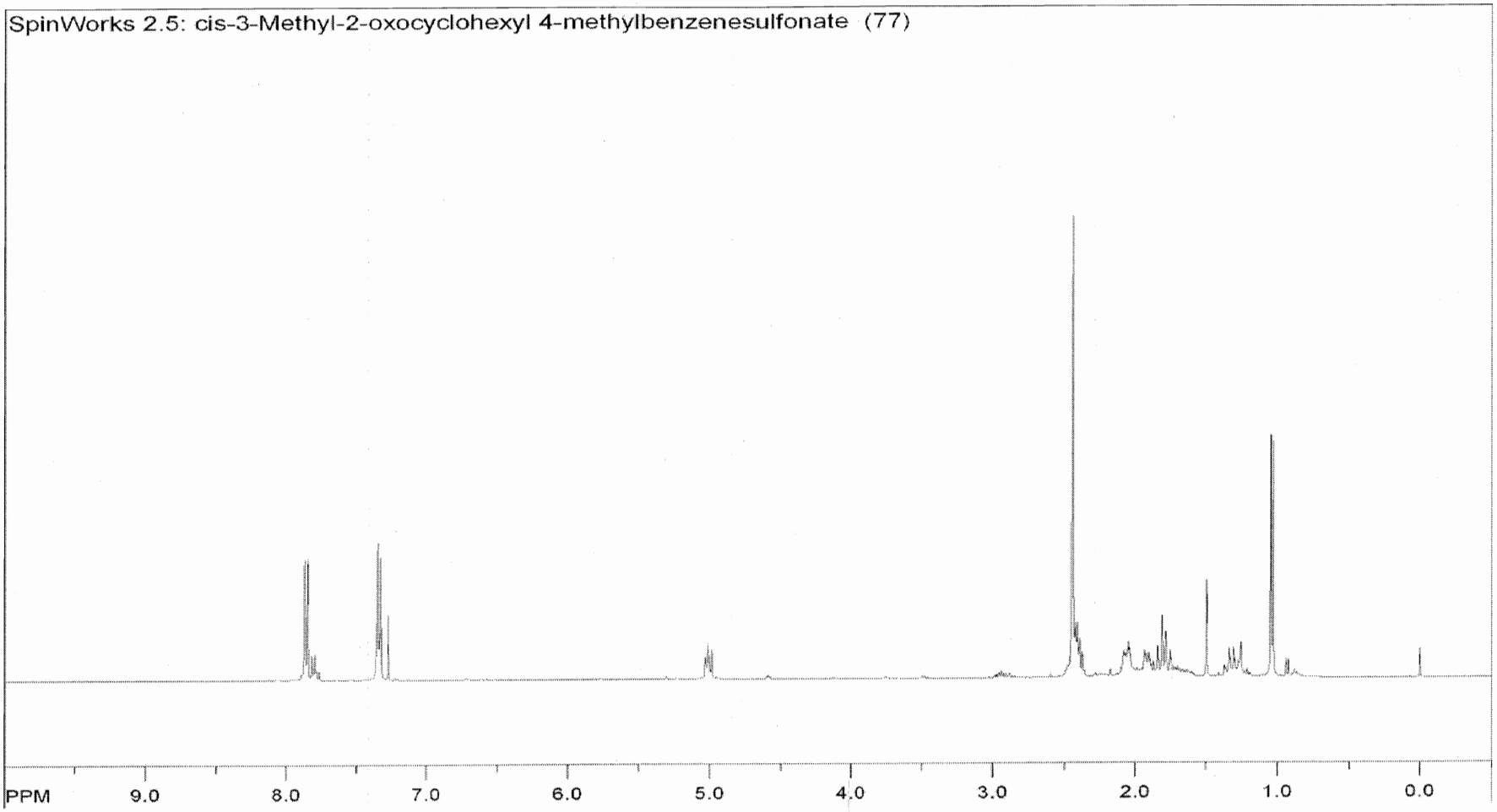

Figure 49. ^{1}H NMR Spectrum of *cis*-3-Methyl-2-oxocyclohexyl 4-methylbenzenesulfonate **(77)**.

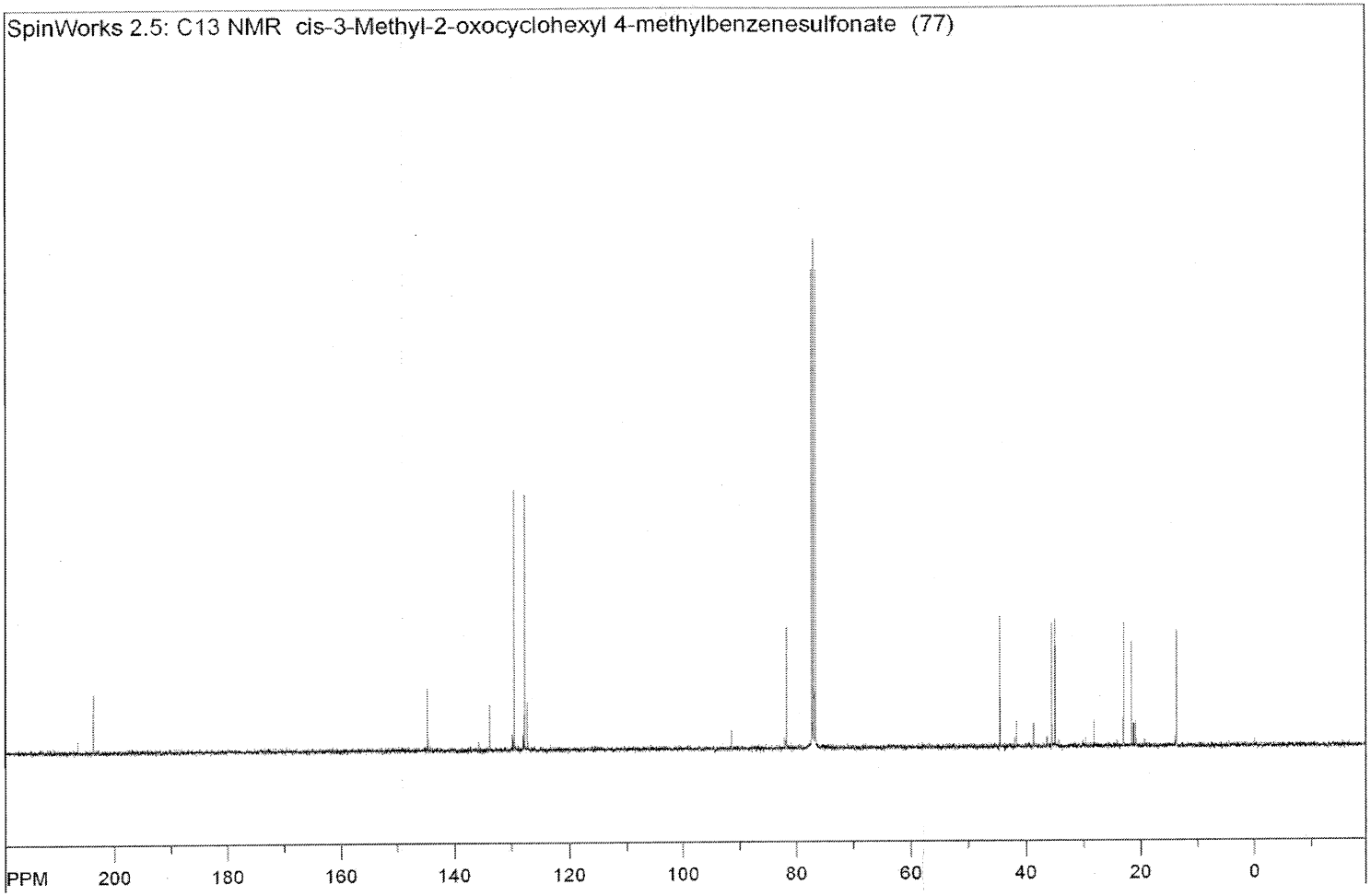

Figure 50. ^{13}C NMR Spectrum of *cis*-3-Methyl-2-oxocyclohexyl 4-methylbenzenesulfonate **(77)**.

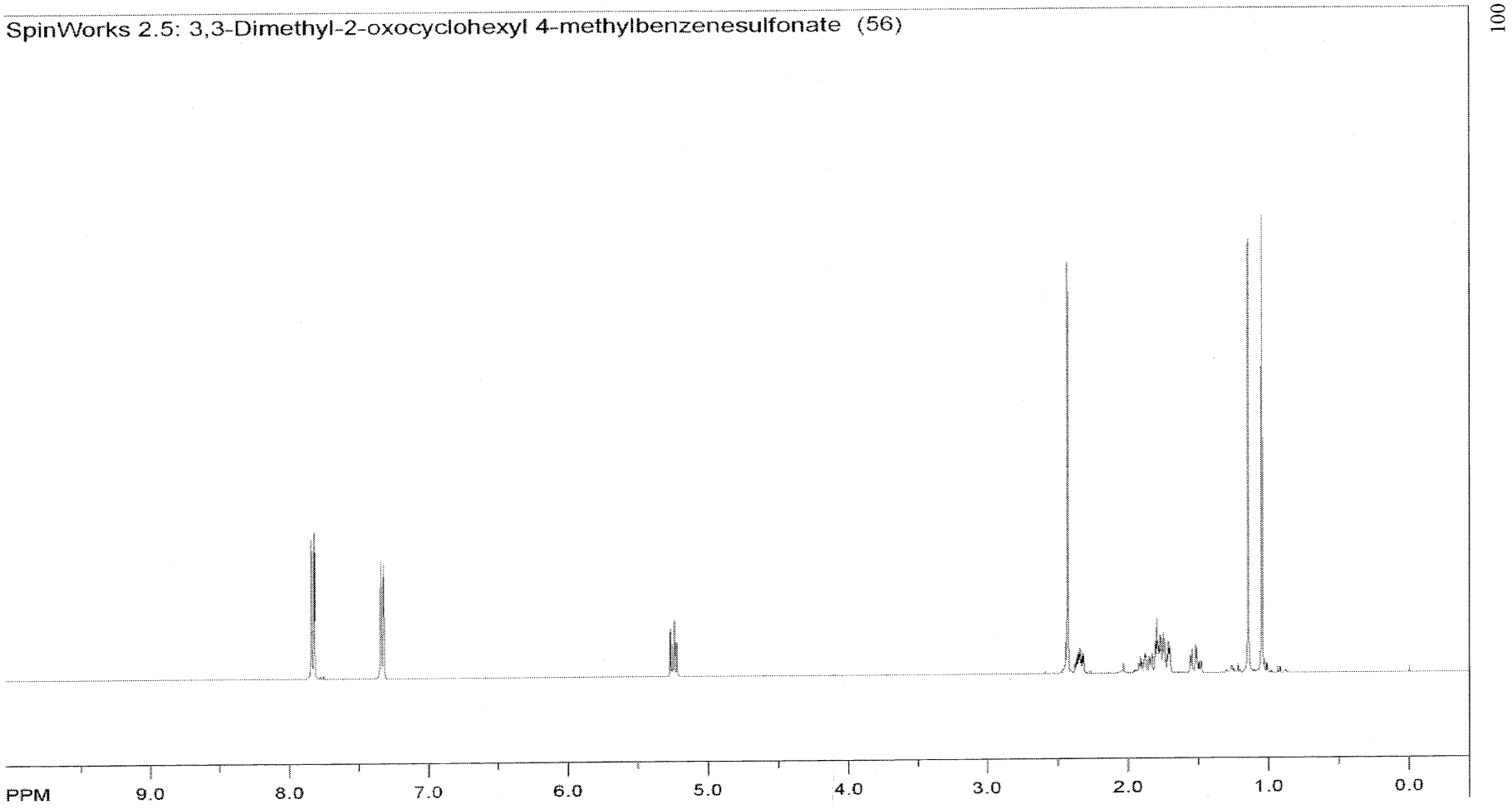

Figure 51. ^{1}H NMR Spectrum of 3,3-Dimethyl-2-oxocyclohexyl 4-methylbenzenesulfonate **(56)**.

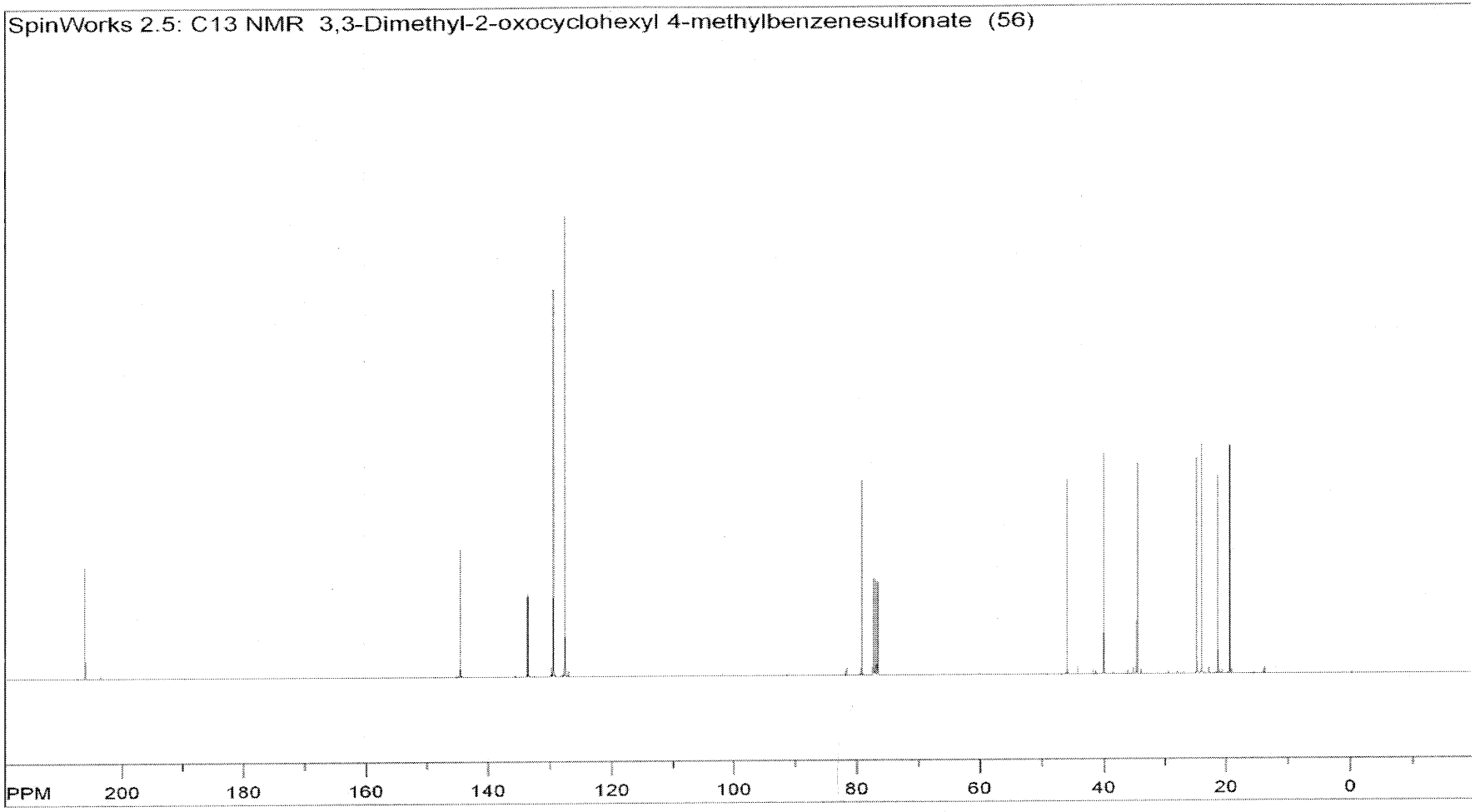

Figure 52. ^{13}C NMR Spectrum of 3,3-Dimethyl-2-oxocyclohexyl 4-methylbenzenesulfonate **(56)**.

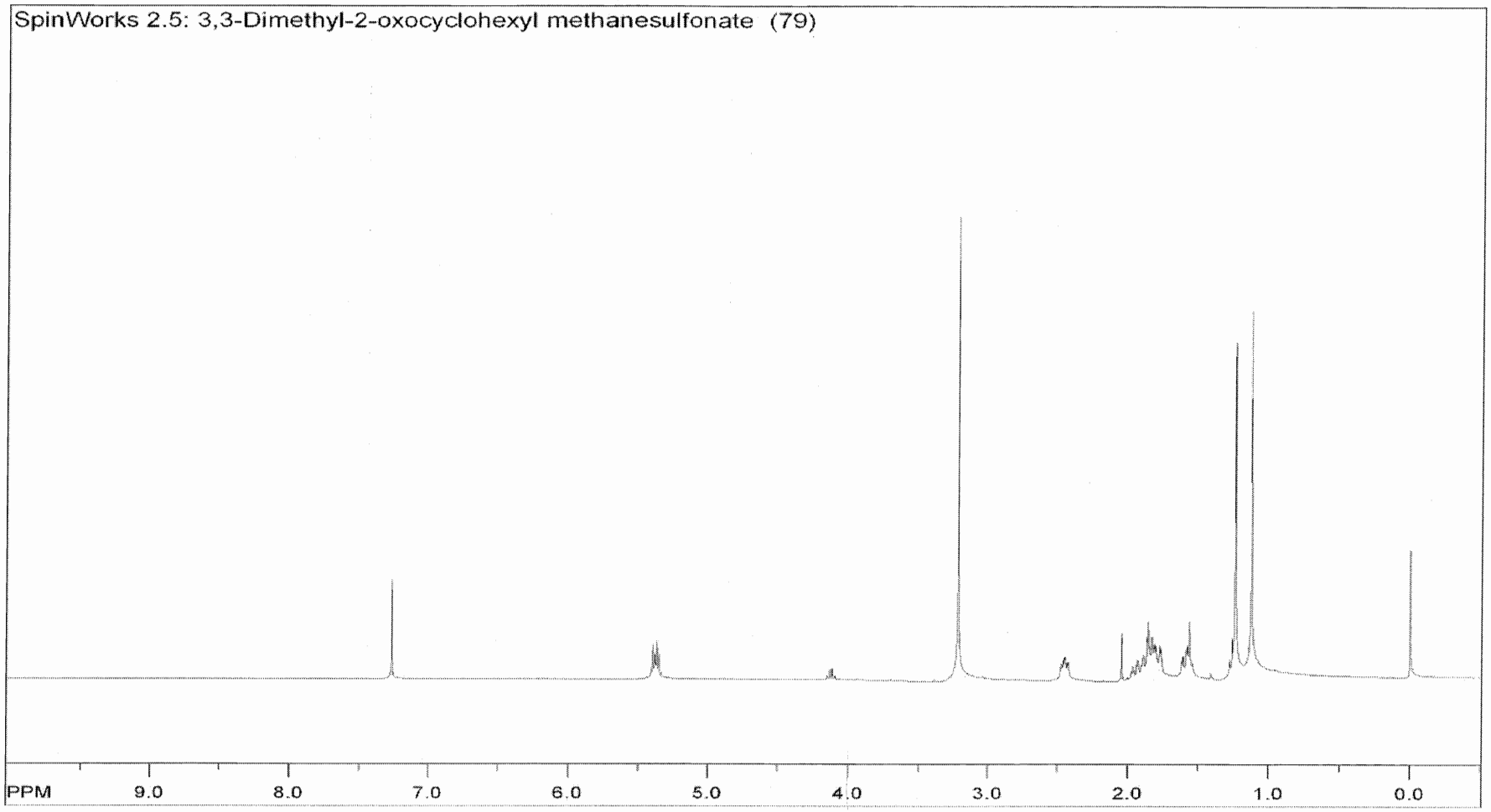

Figure 53. ^{1}H NMR Spectrum of 3,3-Dimethyl-2-oxocyclohexyl methanesulfonate **(79)**.

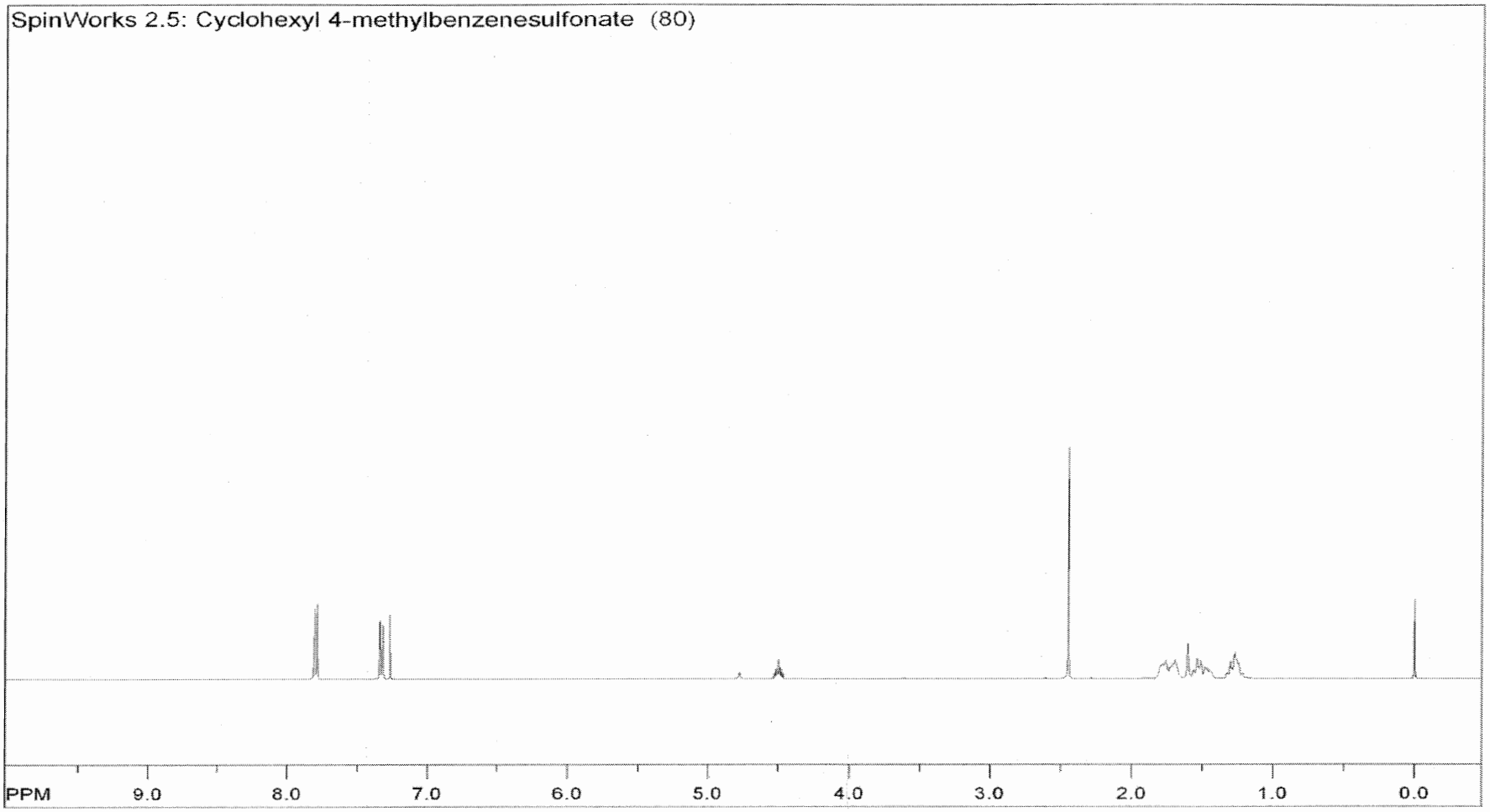

Figure 54. ^{1}H NMR Spectrum of Cyclohexyl 4-methylbenzenesulfonate **(80)**.

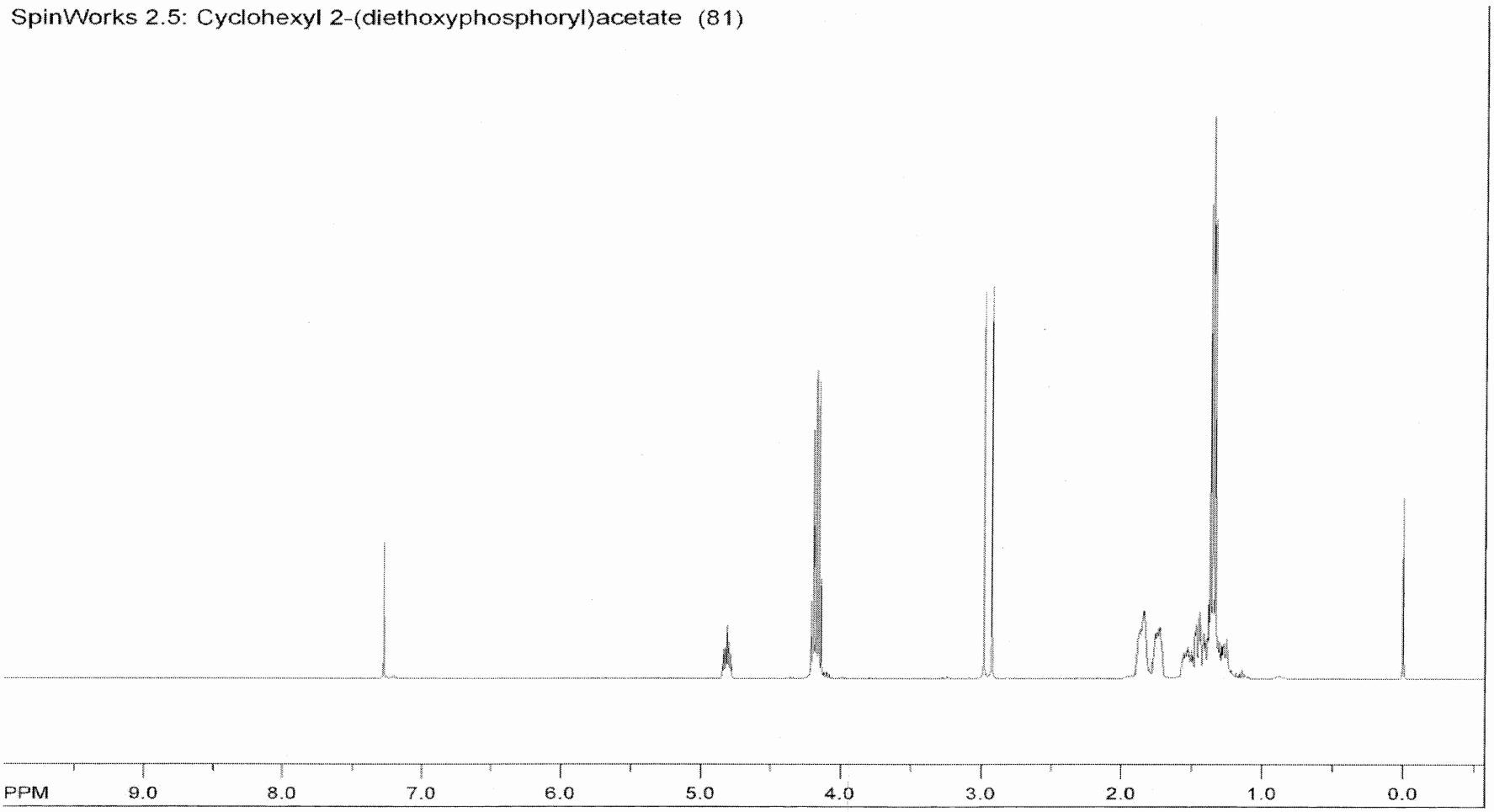

Figure 55. ^{1}H NMR Spectrum of Cyclohexyl 2-(diethoxyphosphoryl)acetate **(81)**.

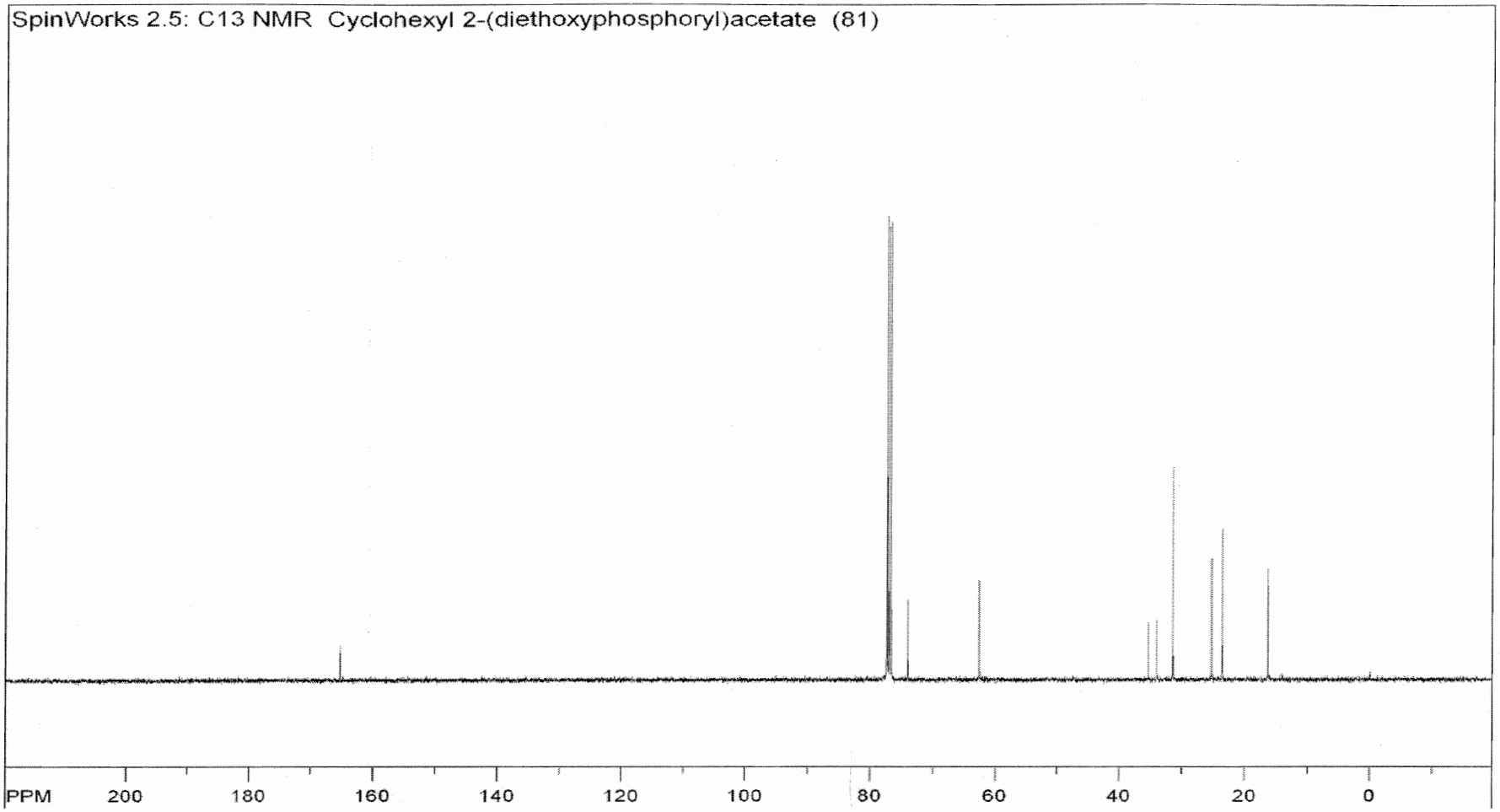

Figure 56. ^{13}C NMR Spectrum of Cyclohexyl 2-(diethoxyphosphoryl)acetate **(81)**.

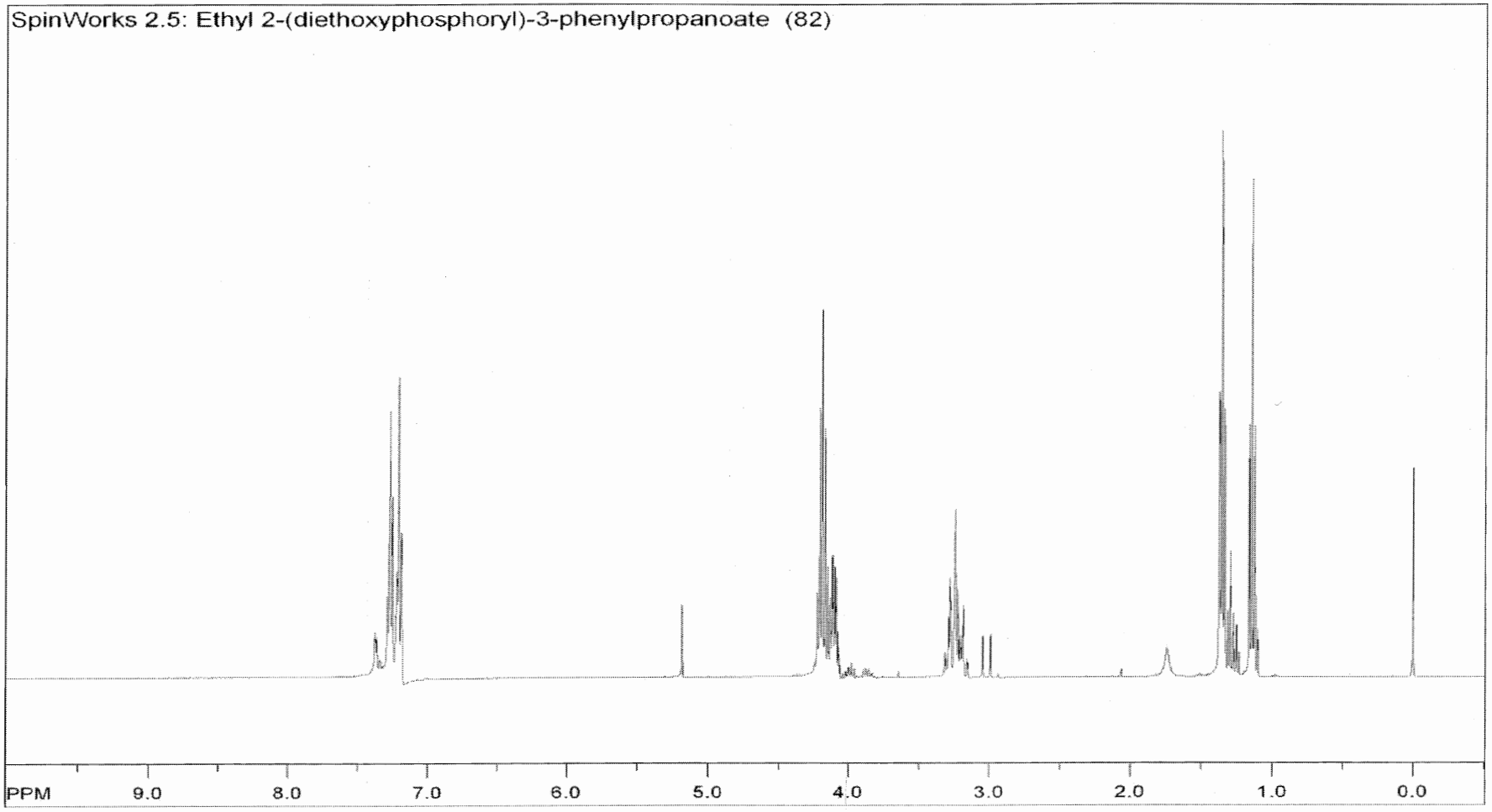

Figure 57. ^{1}H NMR Spectrum of Ethyl 2-(diethoxyphosphoryl)-3-phenylpropanoate **(82)**.

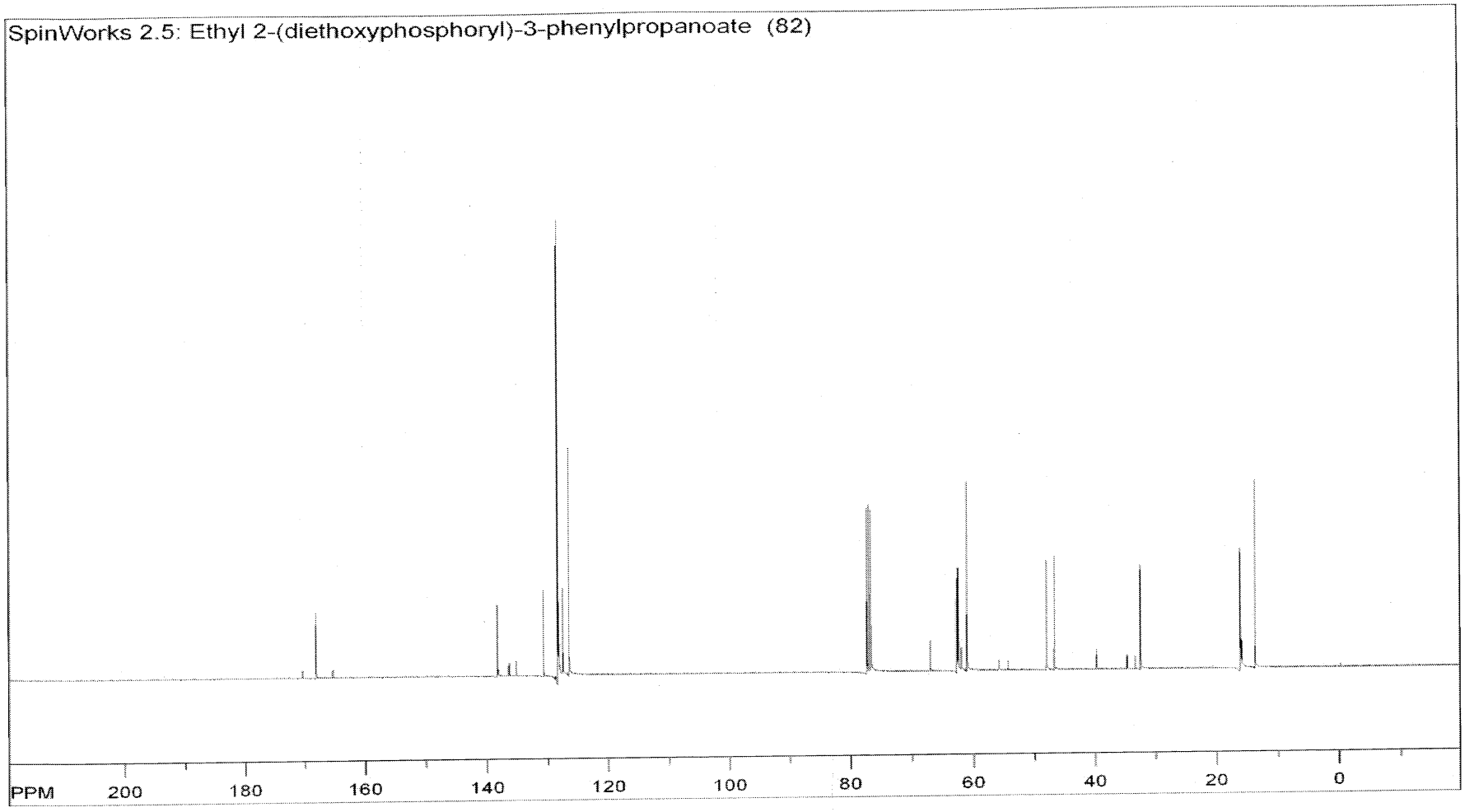

Figure 58. ^{13}C NMR Spectrum of Ethyl 2-(diethoxyphosphoryl)-3-phenylpropanoate **(82)**.

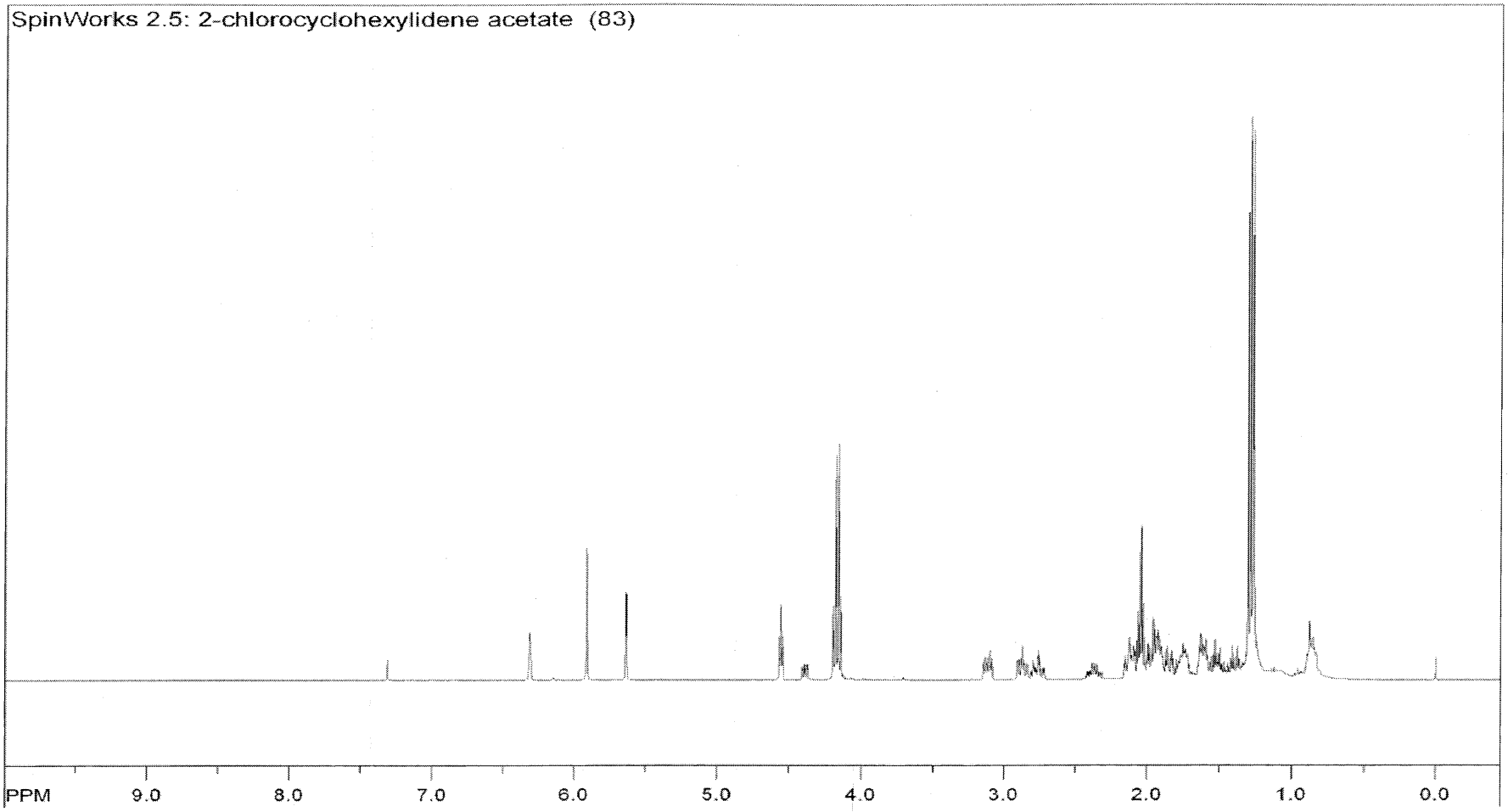

Figure 59. ^{1}H NMR Spectrum of Diethyl 3-(2-chlorocyclohexylidene)-2-oxopropylphosphonate **(83)**.

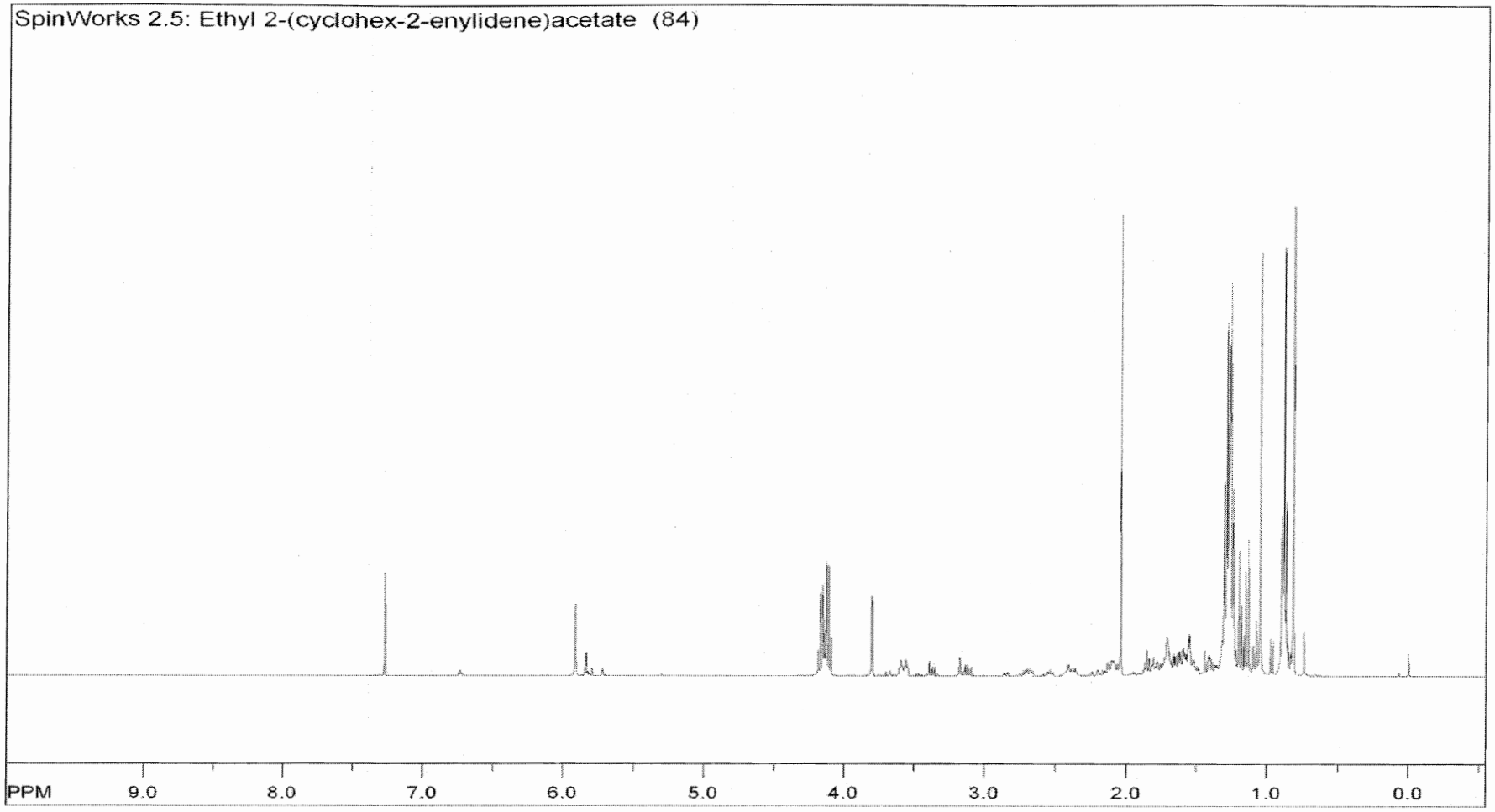

Figure 60. ^{1}H NMR Spectrum of Ethyl 2-(cyclohex-2-enylidene)acetate **(84)**.

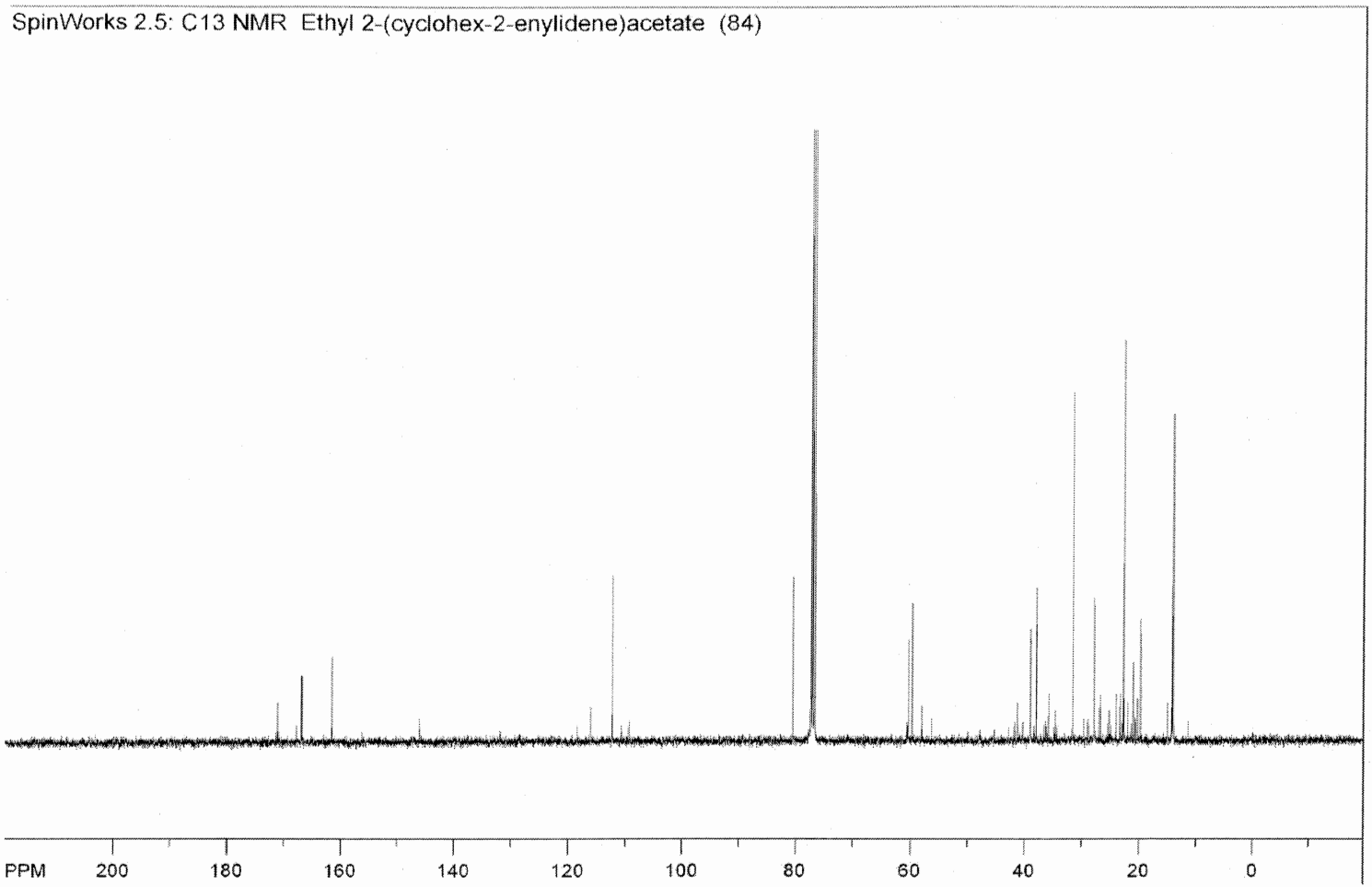

Figure 61. ^{13}C NMR Spectrum of Ethyl 2-(cyclohex-2-enylidene)acetate **(84)**.